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(PROJECT RANCH HAND II)

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

BASELINE MORBIDITY STUDY RESULTS

24 FEBRUARY 1984

Prepared for:
The Surgeon General
United States Air Force
Washington, D.C. 20314

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USAF SCHOOL OF AEROSPACE MEDICINE
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In 1979 the United States Air Force (USAF) made the commitment to Congress and to the White House to conduct an epidemiologic study of the possible health effects from chemical exposure in Air Force personnel who conducted aerial herbicide dissemination missions in Vietnam (Operation RANCH HAND). The purpose of this epidemiologic investigation is to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides. This study uses a matched cohort design in a nonconcurrent prospective setting, incorporating mortality, morbidity, and follow-up studies. This

report presents the results of health information on 2706 Ranch Handers and comparison individuals obtained by questionnaire and 2269 Ranch Handers and comparison individuals undergoing an extensive physical examination.

This baseline 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 disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and to their families at this time.

EXECUTIVE SUMMARY

BASELINE MORBIDITY STUDY

The Ranch Hand II epidemiologic study uses a matched cohort design in a nonconcurrent prospective setting, and incorporates mortality, morbidity, and follow-up studies. The purpose of this report is to present the baseline morbidity study.

The morbidity study design matched each living Ranch Hander (by age, job, and race) to the first living and compliant member of a randomly selected comparison mortality set of 5 individuals, producing a 1:1 contrast. The comparison group was formed from numerous flying organizations which transported cargo to, from, and within Vietnam, but were not involved in aerial spray operations of Herbicide Orange. Of the potential study participants, 99.5% were located. Early in the physical examination phase of the study, it was discovered that 18% of the entire comparison group was ineligible to participate because of inappropriate selection. Thereafter, study eligibility was certified only after a hand-review of personnel records. Next-in-line compliant comparisons entered the study as replacements after fully completing the questionnaire and physical examination. Statistical analyses of these replacement individuals later showed that they differed from the original comparisons in a variety of subtle and often opposite ways. As a conservative measure to avoid possible bias by the inclusion of the replacements in the analyses, a management decision was made to base the statistical tests in this report primarily upon contrasts of the Ranch Hand group to the original comparison group.

The preponderance of data was obtained from the in-home interviews and the physical examination, each conducted under contract to the Air Force by Louis Harris and Associates, Inc., New York NY, and the Kelsey-Seybold Clinic, P.A., Houston TX, respectively. All contacts with the participants were carried out with utmost professionalism and sensitivity. Other morbidity data sources included reviews of medical records, military personnel documents, and birth certificates; in-home questionnaires and telephone questionnaires of the study participant's wives, former wives and, occasionally, their next-of-kin. All aspects of the study were voluntary. As a contract requirement, data collection personnel were blind as to the exposure status of the participants. Ninety-seven percent of the Ranch Handers and 93% of the comparisons participated in the in-home interview. For the physical examination, 87% of the Ranch Handers and 76% of the comparison group participated, a total of 2,272 individuals. This differential attendance at the examination may have introduced a potential participation bias that, in a military population predominantly engaged in flying duties, is multifactorial and complex. All study phases were monitored by stringent quality control standards. Statistical analyses of the data consisted primarily of log-linear models, logistic regression techniques, generalized linear models, matched covariate analyses, and Kolmogorov-Smirnov, chi-square, and t tests.

The physical examination and the in-home questionnaire data were analyzed by major organ system. In terms of general health, more Ranch Handers perceived themselves to be in fair or poor health than did their comparisons. No group differences were detected for hematocrit or percent body fat determinations. Unadjusted group differences in sedimentation rate were not observed; however, significantly more young comparisons had abnormalities in sedimentation rate than did their Ranch Hand counterparts. There were no statistically significant differences in the occurrence of malignant or benign systemic tumors between the groups. One case of soft tissue sarcoma was found in a comparison member. Significantly more nonmelanotic skin cancer was noted in the Ranch Hand group, but these analyses have not yet considered (adjusted for) sunlight exposure, the prime etiology of these cancers. Such nonmelanotic skin cancer (predominantly basal cell carcinoma) is the most common neoplasm in the White population of the United States. Up to the statistical limits of the study there were no consistent data that showed that the Ranch Handers were developing uncommon cancers, or cancer in unusual sites, or at an unusual age. Measures of fertility and reproductive outcome showed mixed results. It is emphasized that the fertility and reproductive results are preliminary at this time as they are based largely upon subjective self reports that await full medical record and birth certificate verification. Four measures of fertility: number of childless marriages, couples with the desired number of children, the infertility index and the fertility index, showed no difference between the Ranch Hand and comparison groups. A semen specimen obtained from those willing and able to provide one showed no group differences with respect to total sperm count or percent abnormal sperm. There were no significant findings in conception outcomes for miscarriages, stillbirths, induced abortions, or live births. For live birth outcomes no differences were observed for prematurity, learning disability, or infant deaths. There was no significant disparity between groups for the classifications of severe or moderate birth defects. By parental history, however, Ranch Hand offspring showed significantly more minor birth defects (birth marks, etc). Reported neonatal deaths and physical handicaps were also significantly excessive in the Ranch Hand group when contrasted to the total comparison group. All fertility and reproductive findings in the Ranch Hand group showed inconsistent relationships to the herbicide exposure index. Medical records and birth certificates are currently being chronicled for complete verification of all historical findings. A comprehensive neurological examination showed no consistent abnormalities in the cranial nerves, peripheral nerves or central nervous system function of the Ranch Handers. As expected, there was a profound influence of diabetes and alcohol in both groups upon numerous neurological tests. Detailed psychologic data were obtained on all participants at both the in-home interview and the physical examination. It is emphasized that the majority of psychological data was derived from self reported responses during interview and has not been fully assessed for the effect of differential reporting. A variety of subjective deficits (fatigue, anger, fear, anxiety, etc) were significantly more common in the high school educated Ranch Handers. Educational level significantly and consistently influenced most subjective test results. In sharp contrast, more objective performance testing by the Halstead-Reitan battery and IQ testing did not reveal any significant intergroup differences. The roles of overreporting and the Post Vietnam Stress Syndrome in these analyses have not as yet been assessed. Liver function tests and clinical history data showed mixed results. Ranch Handers had some elevated liver enzyme tests and lower cholesterol levels. More Ranch Handers were found to have hepatomegaly and verified histories of prior hepatic disease than their counterpart comparisons. Exposure to alcohol, degreasing chemicals, and industrial chemicals in general, influenced the liver test results. Ranch Handers reported significantly more symptoms resembling porphyria cutanea tarda than the comparisons, but these data have not been verified by medical record reviews nor were they substantiated by laboratory testing or by physical examination. Exposure index analyses were essentially negative. In the dermatologic evaluation, no cases of chloracne were diagnosed clinically or by biopsy. A thorough questionnaire analysis of acne showed that the incidence, severity, duration, and anatomic location did not differ between groups, and suggested that the historical occurrence of chloracne was highly unlikely in the Ranch Handers. Evaluation of the cardiovascular system showed equal proportions of abnormalities in blood pressures, electrocardiograms, past electrocardiograms, and heart sounds in both groups. Ranch Handers are not having premature heart attacks or generalized heart disease. However, the Ranch Handers showed significant deficits in 2 specific peripheral leg pulses and all leg pulses as a group. These puzzling findings were highly correlated with age and smoking patterns, and verified past heart disease. The assessment of the immune system by laboratory testing was compromised by excessive test variability. An independent review committee determined which test data were suitable for statistical analysis. As an unexpected finding, the test data were significantly influenced by the age and smoking history of the participant; no group differences were detected after adjustment for these factors. A hematologic test battery revealed three red cell abnormalities in the Ranch Hand group, but these were difficult to place into a clinical or epidemiologic context. Evaluation of renal, pulmonary, and endocrine functions generally disclosed small and inconsistent proportions of abnormalities between groups, and were deemed clinically unimportant. An unrefined assessment of all summed and weighted organ system abnormalities by group did not show an aggregation of multisystem disease or malfunction.

Any interpretation of these study data, in whole or in part, must carefully consider the methodical steps required for a proper inference of causality. It is specifically pointed out that many group differences were largely based upon subjective data, and that a subtle effect of differential reporting is suggested but has not been fully evaluated. For objective data, group differences were generally within normal ranges and were not correlated to the herbicide exposure index, nor fell within the expected latency periods following Vietnam service. The proposed clinical end points of dioxin exposure, chloracne, soft tissue sarcoma, and porphyria cutanea tarda, were not found in the Ranch Hand group (study power limitations recognized). Overall, substantial credence is given to the objective study findings, particularly after observing the consistent duplication of the classical effects of risk factors such as age, smoking, alcohol, etc., in almost all clinical areas. Additional work with these baseline data is still required in the areas of data base refinement, statistical testing and bias analysis, exposure index refinement, establishment of the follow-up examination requirements, and collaboration with other dioxin research studies.

This baseline 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 disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and their families at this time.

PREFACE

In October 1978, the United States Air Force (USAF) Surgeon General made the commitment to the Congress and to the White House to conduct an epidemiologic study of the possible adverse health effects arising from the herbicide exposure of Air Force personnel who conducted aerial dissemination missions in Vietnam (Operation Ranch Hand). The purpose of this epidemiologic investigation is to determine whether long-term adverse health effects exist, and whether they can be attributed to occupational exposure to herbicides and their contaminants. The study protocol for this effort incorporates a matched cohort design placed in a nonconcurrent prospective setting. The study approach includes mortality, morbidity, and follow-up elements linked tightly in time in order to produce the most data in the shortest time. The study addresses the question: Have there been, are there currently, or will there be any adverse health effects among former Ranch Hand personnel caused by repeated occupational exposure to 2,4,5-Trichlorophenoxyacetic acid (2,4,5,-T) containing herbicides and the contaminant, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)? At the request of the Principal Investigators (see Appendix I) the study protocol was extensively and independently reviewed. The review agencies included: The University of Texas School of Public Health, Houston TX; the USAF Scientific Advisory Board; the Armed Forces Epidemiological Board; and the National Research Council of the National Academy of Sciences. In 1980, the Science Panel of the Agent Orange Working Group was created as an additional peer review agency. This group, redesignated as the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, has consented to the oversight responsibility of the Ranch Hand study and continues to monitor the conduct of this epidemiologic investigation (see Appendix II).

The Air Force Health Study (Ranch Hand II) protocol emphasizes the suboptimal statistical power of the mortality study. The mortality study was motivated by the desire to use a full spectrum epidemiologic approach to the herbicide question. Additionally, the investigators were scientifically obliged to pursue the mortality study because of previous and emerging studies (some with small sample sizes) which suggested the possibility of a soft tissue sarcoma end point (Honchar, 1981; Hardell, 1979; Erikson, 1979). Within the inherent sample size limitation of the Ranch Hand population, detection of such a rare condition will be missed unless there is marked case clustering and correspondingly high relative risks.

Also, because of sample size limitations as well as the myriad of proposed clinical end points, a case-control design was not entertained. In the morbidity phase of the study, the investigators have attempted to enhance statistical power and analytic sensitivity where possible by using (1) precise matching procedures with a replacement strategy to maintain statistical power while averting a loss-to-study bias, (2) exacting quality control procedures, (3) mortality-morbidity linkages, (4) a lengthy follow-up study, (5) state-of-the-art statistical methodology, (6) continuously distributed physical examination variables, and (7) data collection focused on verifiable end points.

The mortality analyses have not revealed any adverse death experience in the herbicide/dioxin exposed cohort. The results of the analyses were consistent: at this time, there is no indication that Ranch Hand personnel have experienced any increased mortality or any unusual patterns of death in time or by cause. They are not dying in increased numbers, at earlier ages, or by unexpected causes.

The fact that only a relatively small number of Ranch Hand deaths were available for analysis is reassuring in itself. However, the fact that adverse effects have not yet been detected does not imply that an effect will not become manifest at a future time or after covariate-adjusted analyses. For this reason, further analyses are intended and mortality in the study population will be ascertained annually for the next 20 years.

The morbidity portion of the study was conducted in two phases; an in-home, face-to-face interview, and a comprehensive physical and psychological examination. Both phases were conducted by civilian organizations under contract to the Air Force, using materials and procedures prescribed by the contract. One thousand, one hundred seventy four (97%) of the Ranch Hand group and 1,156 (93%) of the initially selected comparison group participated in the questionnaire. An additional 376 comparison subjects were interviewed as replacement subjects, bringing the total number of comparison participants to 1,532. Two thousand, seven hundred eight current and former wives of the study participants were interviewed. One thousand forty five (87%) of the Ranch Hand group participated in the physical examination, and 936 (76%) of the initially selected comparison subjects participated. Two hundred eighty-eight replacement subjects also participated in the examination process, giving a total of 2,269 participants, resulting in 1,024 matched pairs for analysis.

The first chapter of this report is devoted to a discussion of the background of the study and the next seven chapters present a summary of the methodology used in gathering, analyzing, and interpreting the data. The results and discussion of these analyses, organized by organ system and/or disease end point, are contained in the remaining chapters.

This report assumes that readers are familiar with statistical and epidemiologic techniques. It also assumes that the reader has a familiarity with the herbicide/dioxin issue and a detailed knowledge of the protocol of the Air Force study, the baseline questionnaire, and the baseline mortality results. In the interest of brevity, the reader is referred to the protocol published as US Air Force School of Aerospace Medicine Technical Report 82-44, the baseline questionnaires published as US Air Force School Aerospace Medicine Technical Report 82-42, and the Baseline Mortality Study Results, 30 June 1983. These reports are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161.

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The Ranch Hand Association and its elected officers, for sustained encouragement of the study, assistance in population ascertainment, and camaraderie and patriotism which contributed to unparalleled participation rates.

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The over 100 professionals, consultants, technicians, military and civilian, whose dedication and hard work over the past five years have made this report possible.

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Chapter I

BACKGROUND

In January 1962, President John F. Kennedy approved a program to aerially disseminate herbicides in the Republic of Vietnam (RVN). This program, code named Ranch Hand, was conducted in support of tactical military operations and had 2 missions: defoliation and crop destruction. During the 9-year duration of the operation, approximately 19 million gallons of herbicides were sprayed on an estimated 10-20% of South Vietnam (Young, 1978; Buckingham, 1982). Of the 6 herbicides used, Herbicide Orange was the primary defoliant, and approximately 11 million gallons were dispersed. Because of the controversial nature of the mission and enemy propaganda which raised political sensitivity to chemical warfare charges, the Ranch Hand operation was subjected to intense scrutiny from the start. Initial concerns were focused on the military, political, and ecological ramifications of the spray operations (Buckingham, 1982). Since 1977, the issue has shifted to a health concern. Numerous U.S. military personnel from all services have claimed exposure to herbicides, particularly Herbicide Orange and its dioxin contaminant, during their duty in the RVN. These possible exposures, coupled with claims of attributable adverse health, have resulted in class action litigation and substantial controversy within the Government, Veterans' groups, the scientific community, and the public.

The U.S. Air Force Medical Service expressed its concern for the health of Air Force personnel exposed to herbicides in October 1978, when the Deputy Surgeon General, Major General Garth M. Dettinger, told the U.S. House of Representatives' Veterans Affairs Committee that the USAF would evaluate the health of Ranch Hand personnel. An epidemiologic study design was prepared by the USAF School of Aerospace Medicine to meet this commitment. Following extensive peer review, a final study protocol was published, (Lathrop, Wolfe, Albanese, Moynahan, 1982) and the epidemiologic study was initiated.

Since 1978, numerous governmental agencies, universities, and industrial firms have planned or launched additional animal and human studies. An immediate scientific issue was identified in these studies, specifically, the characteristics of the RVN exposure. Succinctly, these questions are: (1) Who was exposed to which herbicide? (2) By what means can these individuals be accurately identified for study? (3) How much, or to what degree, were they exposed (route of administration, influence of personal hygiene measure, etc.)? These areas merit careful consideration because the process of population or exposure estimation may generate substantial misclassification errors that would call for inordinate sample sizes in a contemplated study. Government and civilian scientists and the Congress have recently inquired of the Air Force Health Study as to whether it might clarify the exposure controversy in ground personnel. The answer is a qualified yes.

The dose-response principle suggests that if the Ranch Hand population was more exposed to herbicides and dioxin than ground personnel, then the Ranch Handers should manifest stronger and/or earlier indications of adverse health, if they have occurred or will occur in the future. This principle is constrained by statistical power but, as noted in Chapter VII, the Ranch Hand morbidity study has substantial power in some clinical areas. The fact is that the average Ranch Hander was substantially exposed to the herbicides and dioxin (relative to other military personnel in RVN) on almost a daily occupational basis. Exposure calculations have estimated that an average Ranch Hander in his tour received, at a minimum, 1000 times more exposure to Herbicide Orange than would an average unclothed man, standing in an open field directly beneath a spraying aircraft. Unfortunately, the relative degree of Ranch Hand exposure vis-a-vis ground personnel has been consistently undervalued, and even reversed by various advocacy groups and the media.

It is our firm belief that the Ranch Hand population is the most herbicide-exposed military cohort to have served in the RVN. The fact of the unequivocal exposure in a totally ascertained population, when matched to an equally clear-cut nonexposed cohort, provides as ideal an epidemiologic setting as possible from a wartime environment. Findings of adverse health, or lack thereof, in the Ranch Hand group should serve as a significant epidemiologic pointer to the health effects issue in exposed ground personnel.

STUDY DESIGN

This study uses a matched cohort design in a nonconcurrent prospective setting, incorporating mortality, morbidity, and follow-up studies. A detailed population ascertainment process has identified 1269 Ranch Hand personnel who served in the RVN during the period 1962-1971. A comparison group was formed by identifying all individuals assigned to selected Air Force organizational units with a mission of flying cargo to, from, and in the RVN during the same period. Complete details on the selection of the comparison population are cited in the study protocol. By a computerized nearest neighbor selection process, up to 10 comparison individuals were matched to each Ranch Hander by job category, race, and age to the closest month of birth. An average of 8.2 comparison individuals for each Ranch Hander were determined by record review to be fully suitable for study. From each matched comparison set, 5 individuals were randomly selected for the mortality study (1:5 design). Results of the Mortality Study were released to the public on 30 June 1983. Each living Ranch Hander and the first living member of his comparison set were selected to participate in a morbidity study consisting of an in-home interview and a comprehensive physical examination. Data collection for both the questionnaire and physical examination was accomplished by contract. The follow-up study consists of mortality and morbidity components. Every Ranch Hander and his set of comparisons will be the subjects of annual mortality updates for the next 20 years, so that any emerging mortality patterns or disease clusters may be detected with maximal sensitivity. In addition, follow-up questionnaires and physical examinations will be offered to all participants in subsequent years 3, 5, 10, 15, and 20, in order to bracket the latency periods associated with possible attributable disease.

Chapter II

POPULATION

The exposed population, termed "Ranch Hand", was defined as those individuals who were formally assigned to the USAF organizations responsible for the aerial dissemination of herbicides and insecticides in the Republic of Vietnam from 1962 through 1971. These individuals were identified from historical data sources (morning reports, military personnel records, and historical computer tapes) at the National Personnel Records Center (NPRC), St. Louis, Missouri and the USAF Human Resources Laboratory, Brooks Air Force Base, Texas. A total of 1264 Ranch Hand personnel were identified through this initial process. The comparison population was defined as those individuals who were assigned to a variety of cargo-mission organizations throughout Southeast Asia during the same time period. Cargo-mission aircrew members and support personnel were selected because of sufficient population size, similar training and military background experiences, and psychological similarities to the Ranch Hand group. The comparison population was not occupationally exposed to herbicides or insecticides in the Republic of Vietnam. Identification of this population (24,971 individuals) was completed using the same historical data sources as were used to identify the Ranch Hand population.

1. Original Match

Before matching the Ranch Hand and comparison populations, all individuals killed in action (KIA) were removed from the data base. The rationale for their removal is the assumption that combat death in the Ranch Hand group was independent of herbicide exposure. Twenty-two Ranch Handers were identified as KIA. KIA's were also removed from the comparison group for comparability purposes. The remaining Ranch Hand population was matched to the comparison population with an iterative nearest-neighbor computer program (Lathrop, Wolfe, Albanese, Moynahan, 1982). This procedure attempted to match 10 comparison individuals with each Ranch Hander to the closest month of birth, race (Black versus non-Black), and occupational code (1-officer--pilot, 2-officer--navigator, 3-officer--nonflying, 4-enlisted--flyer, and 5-enlisted--ground). Table II-1 presents the total number of study participants by occupation code, and race.

Table II-1

DISTRIBUTION OF THE INITIALLY MATCHED STUDY POPULATION BY OCCUPATION AND RACE

Occupation Code		Number: Ranch Hand	Number: Comparisons
Non-Black			
1 - Officer-Pilot		349	3318
2 - Officer-Navigator		78	780
3 - Officer-Nonflying		25	250
4 - Enlisted-Flyer		187	1871
5 - Enlisted-Ground		528	5277
	Subtotal	1167	11,496
Black			
1 - Officer-Pilot		6	16
2 - Officer-Navigator		2	20
3 - Officer-Nonflying		1	5
4 - Enlisted-Flyer		15	146
5 - Enlisted-Ground		51	510
	Subtotal	75	697
TOTAL		1242	12,193

The total Ranch Hand population consists of 37% officers and 63% enlisted personnel. Seventy-seven percent of the total Ranch Hand officer population are pilots, 17% navigators, and 6% other officers; 26% of the total Ranch Hand enlisted population are flight engineers and 74% are enlisted nonflying personnel.

Following the match, the majority of Ranch Handers had 10 comparisons. The exceptions were the non-Black pilots who had a mean of only 9.5 comparisons per exposed individual due to the extreme ages of several individuals, and the Black pilots and other Black officers who had means of 2.7 and 5.0 comparisons, respectively. Six percent of the exposed population was found to be Black and 88% of this population was enlisted. Of these enlisted personnel 77% were occupational code 5, Enlisted - Other. All subjects are males. The mean age of the study subjects is approximately 45 years.

2. Ineligibility

In December 1981, the USAF Principal Investigators were advised by the questionnaire contractor that several comparison subjects had reported no experience in Southeast Asia, suggesting that inappropriate selection of some comparison subjects had occurred. Manual review of the comparison populations military personnel records revealed that 18% of the 12,193 comparison individuals in the original match were indeed ineligible for study. The inadvertent inclusion of several non-Southeast Asia military organizations had resulted in the selection of these inappropriate individuals. The percent loss to the total 1:10 matched comparison population due to ineligibility by occupation code, race, and average age is presented in Table II-2.

Table II-2

PERCENT INELIGIBLE BY OCCUPATION CODE AND RACE,
WITH AVERAGE AGE OF INELIGIBLES BY OCCUPATION CODE

Race	Percent Loss and Occupation Code Counts of Ineligible Comparisons: 1	2	3	4	5	TOTAL
Non-Black	(12%) 414	(12%) 90	(34%) 84	(12%) 230	(24%) 1254	(18%) 2072
Black	(13%) 2	(5%) 1	(60%) 3	(10%) 15	(23%) 115	(20%) 136
Total	(12%) 416	(11%) 91	(34%) 87	(12%) 245	(24%) 1369	(18%) 2208
Average Age in Years (as of Nov 83)	48	48	46	48	42	44

Table II-2 shows that of the 18% loss to the total matched population 18% occurred in the non-Black and 20% occurred in the Black population subsets. Thirty-four percent of all participants in occupation code 3 (nonflying officer) and 24% in occupation code 5 (nonflying enlisted) were lost due to ineligibility. The losses from occupation code 5 clearly exceed the losses in the other 4 categories. The nonflying enlisted individuals were on average the youngest (42 years) while the flying officer and flying enlisted categories were on average the oldest (48 years).

A full log-linear analysis (see chapter VII) with all three matching variables included simultaneously was not performed because of the many small cell counts involved. A log-linear model fitted to the three-way frequency table based on eligibility, occupation code, and race, revealed a significant association of eligibility with occupation code (P<.001, adjusted), but not with race (P=.41, adjusted).

Because the comparison ineligibility problem was identified after the morbidity study questionnaire and physical examination contracts had been implemented, the ineligible comparisons were removed from the matched cohort and the remaining comparison matrix was collapsed to fill the vacancies created by these removals. This process is characterized in Figure II-1.

Figure II-1

REMOVAL OF THE INELIGIBLE COMPARISONS
AND THE SHIFT LEFT

RANCH HAND	COMPARISONS									
RH	$\cancel{C_1}$	C_2	$\cancel{C_3}$	C_4	C_5	C_6	$\cancel{C_7}$	C_8	C_9	C_{10}

This figure shows a hypothetical Ranch Hander (RH) and his 10 comparison subjects (C_1-C_{10}). The C_1, C_3 and C_7 were found to be ineligible and removed. All remaining eligibles were then shifted to the left, i.e., C_2 became C_1, C_4 became C_2, etc. Following the removal of all ineligible subjects, the study was reduced to a 1:8 design. The ineligible selection, the shift left and the subsequent comparison population reduction was presented to the Advisory Committee in 1982. This group felt that the impact of group ineligibility on the study design was negligible; however, subsequent analysis demonstrated a potential impact on inferential reliability (See Chapter V, Compliance and Bias). Statistical considerations required that the shifted population be flagged and analyzed independently of the original comparisons. The data in this report have been primarily analyzed using the original comparisons in an attempt to best describe potential herbicide effects. Wherever possible, analyses using the entire comparison population are also included.

During the conduct of the initial morbidity study 5 additional Ranch Handers were identified through personnel record sources and Veterans Administration Education Benefits and Financial Records. These 5 individuals had not been identified earlier because the majority of their military personnel records had been destroyed in a fire at the NPRC in St. Louis. Three of these 5 were newly discovered Ranch Handers and 2 were comparisons who were subsequently identified as Ranch Handers. Ten additional Ranch Handers were identified following the completion of the morbidity study. These individuals will be included in the follow-up study. No attempt was made to select comparisons for these new Ranch Handers. During the removal of ineligible subjects, 1 Ranch Hander, a Black officer pilot, lost his only comparison and remains unmatched, giving a total of 16 unmatched Ranch Handers, of which 6 are in this study.

At the time of morbidity study implementation there were 1,241 Ranch Handers matched to 1,026 original and 212 shifted comparisons. Three eligible shifted comparisons were deleted following data collection. The comparison population (C_1) eligible for data collection for the baseline morbidity effort is presented in Table II-3 by occupation group and nature of the comparison group, i.e., original or shifted.

Table II-3

COMPARISON POPULATION ELIGIBLE FOR THE MORBIDITY STUDY
BY OCCUPATION CODE AND NATURE OF COMPARISON GROUP
I.E., ORIGINAL OR SHIFTED (C_1)

Occupation Code		Original Comparisons (O)	Shifted Comparisons (S)	Total
Non-Black				
1		307	41	348
2		72	6	78
3		13	12	25
4		169	18	187
5		405	122	527
	Subtotal	966	199	1165
Black				
1		5	0	5
2		2	0	2
3		1	0	1
4		15	0	15
5		37	13	50
	Subtotal	60	13	73
	TOTAL	1026	212	1238

Sixty-four percent of the shifted comparison population is in occupation code 5 (Enlisted-ground). All Black shifted comparisons are in this group, as well.

The study protocol estimated that 39% of the entire Ranch Hand population would complete the physical examination portion of the morbidity study. This initial estimate of compliance was based on an estimate of the influences of status (military active duty, military retired, separated and flying) on the individual who could not be guaranteed confidentiality of medical findings. Status also influenced locatability. Active duty and military retired personnel are located through military data sources, while separated individuals must be located through civilian sources. The status and the flying category of the Ranch Hand and comparison population are presented in Tables II-4 and II-5.

Table II-4

STATUS OF THE RANCH HAND
AND MATCHED MORBIDITY COMPARISON POPULATION (C_1)

Status	Ranch Hand	Comparison Original	Comparison Shifted	Comparison Total
Active Duty	185	157	27	184
Retired From Military	576	510	85	595
Separated	442	359	100	459
TOTAL	1203*	1026	212	1238

*39 Ranch Hands were deceased at the initiation of the morbidity study.

Table II-4 demonstrates that 48% of the population is retired from the military; 15% remain on active duty; and 37% are separated. Those individuals currently holding military or civilian flying certificates are presented in Table II-5.

Table II-5

COUNTS OF THE INDIVIDUALS HOLDING MILITARY AND CIVILIAN
FLYING CERTIFICATES, THE RANCH HAND AND MATCHED COMPARISON POPULATION (C_1)

Status	Ranch Hand	Comparison Original	Comparison Shifted	Comparison Total
Military Flying	82	78	12	90
Federal Aviation Admin Certificate	128	128	16	144
TOTAL	210	206	28	234

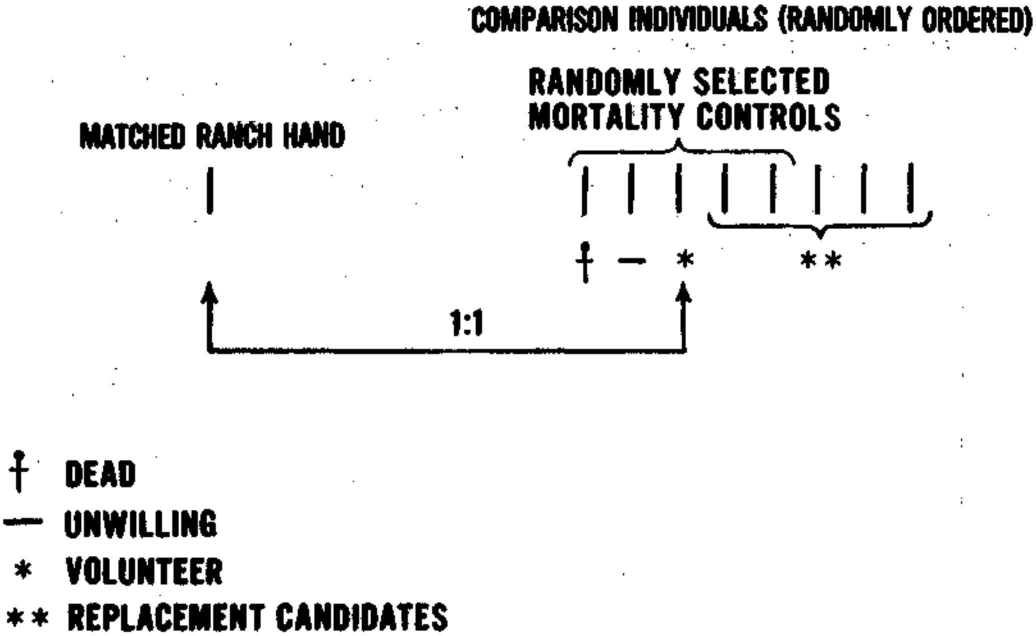
This table shows that 17% (210/1203) of the Ranch Handers and 19% (234/1238) of the total C_1 population presently have military aviation codes or Federal Aviation Administration (FAA) certificates that define active participation in aviation. Twenty percent (206/1026) of the original and 13% (28/212) of the shifted comparison population hold FAA certificates.

3. Study Selection

The study protocol defines the morbidity population as all living Ranch Handers and their first randomly selected, alive and compliant comparison. The selection procedure for the questionnaire and physical examination is presented in Figure II-2.

Figure II-2

SELECTION PROCEDURE FOR THE QUESTIONNAIRE, PHYSICAL EXAMINATION, AND FOLLOW UP STUDY



In this example, the first randomly ordered comparison was found to be dead. The second was contacted but unwilling to participate, and the third volunteered to participate in the morbidity study. This process resulted in a third comparison subset, the replacement population. As shown in Figure II-2, this population resulted from the refusal of the original and shifted comparisons to participate in the morbidity study. The study protocol required that the replacement comparisons be matched to the noncompliant individuals on health perception and that they be treated separately in the statistical analyses. In actuality, they were not matched on health perception but were the first volunteers in the randomly ordered mortality sets following original comparison refusals. Because the health perception of the replacement was not matched to the original, comparison subject data analyses and inferences based on these analyses will only be reported for the original and total comparison populations. In this design, deceased Ranch Handers cannot be replaced for physical exam, while deceased comparisons can be replaced due to the one-many matching. This disparity could lead to inferential bias if cause-specific death rates differ in the two groups. Thus far, these rates are not significantly different.

This epidemiologic study was designed as a matched cohort design. There were 1241 Ranch Handers matched to comparisons by age, race and occupational category at the initiation of the morbidity study. The matched comparison population consisted of 1026 original and 212 shifted comparisons. Three ineligible shifted comparisons were deleted following data collection. The shifted group resulted from inappropriate selection, removal, and shifting left of the comparison population. Additionally there were 16 Ranch Handers who could not be matched. Ninety-four percent (1171/1247) of the study population is non-Black. The average age of the population is 45 years and 15% (185/1203) remain on active duty. Eighteen percent (210/1203) of the Ranch Handers and 19% (234/1238) of the total comparison group have either military flying duties or FAA certificates that denote active participation in aviation. There were 39 known deceased Ranch Handers. As a study requirement, all morbidity study comparisons were alive at the initiation of the morbidity effort. In summary, 1208 living Ranch Handers and 1238 original and shifted comparisons were entered into the morbidity study.

Chapter III

QUESTIONNAIRE METHODOLOGY

1. Introduction

The purpose of the extensive questionnaire was to collect data that could be analyzed for the subjective presence of adverse health effects that might be related to herbicide exposure. The study protocol required that all living exposed subjects and their primary comparisons be offered a comprehensive personal and family health questionnaire administered in the subject's home by a civilian contractor experienced in survey research. The personal nature of the information, peer review recommendations, and the study protocol called for face-to-face interviewing techniques (Herman, 1977; Fry, 1958). In addition to the study participants, the contractor was also required to interview the participant's current and former wives, as well as the first order next-of-kin of deceased individuals to obtain complete morbidity data. Whenever individuals, their spouses, or next-of-kin would not consent to participate in a face-to-face interview, attempts were made to collect the information by telephone (Colombotos, 1969). For the individual who absolutely refused to participate in this data collection process an abbreviated or noncompliant telephone interview format was designed and its use was attempted (Simon, 1974). This chapter discusses the development and the implementation of the questionnaires used in the study.

2. Questionnaire Development

The data collection instruments for the morbidity study were developed and implemented by three separate contracts. The first of these, awarded to Research Statistics, Inc of Houston, Texas in 1979, developed a statement of work (SOW) which described, in survey research terms, the questionnaire requirements to support the effort. This SOW was used as the basis for the questionnaire development contract which was later awarded to the National Opinion Research Center (NORC) of New York, New York. The questionnaire instruments were developed by NORC in cooperation with the Principal Investigators and included questions concerning a broad range of health effects. The choice of specific effects included in the instruments was based on scientific studies of humans and animals exposed to phenoxy herbicides and dioxins. Hypothetical health effects based on studies in biochemical and biological systems were also included. In addition, veterans' complaints and the public's perception of the health effects of these chemicals were also considered. Questions were designed to allow the maximum degree of data verification by physical examination and medical and personnel record reviews. At the suggestion of NORC, portions of previously field-tested questionnaires were incorporated in the study instruments to maximize the validity of the questionnaires. The sources of the field-tested questionnaires are presented in Table III-1.

Table III-1

SOURCES OF QUESTIONNAIRE ITEMS

Section of USAF Health Study Questionnaire	Field Tested Questionnaires
Marital History	The Lives of Women in American Society (Institute of Human Reproductive Studies; Columbia University School of Public Health, Denise B. Kandel)
Pregnancy outcomes	The Lives of Women in American Society
Conception difficulty	National Survey of Family Growth Cycle, (National Center for Health Statistics; Vital and Health Statistics, Series 2, #76 January 1978 William F. Pratt)
Education	General Social Survey (National Opinion Research Corporation, Roper Public Opinion Research Center, University of Conneticut 1981, James A. Davis)
Occupation	General Social Survey
Health outcomes	Procedures and Questionnaires of the National Medical Care Utilization and Expenditure Survey (National Center for Health Statistics; Series A, Methodological Report #1, 1980 Robert R. Fuchsberg)
Smoking, drugs	Drug Abuse Reporting Program (Institute of Behavioral Research, Texas Christian University, 1976 Saul B. Sells)
Drinking	Drug Abuse Reporting Program
Erosion of cognitive abilities	Drug Use Vietnam Veteran 1972; Resurvey of Vietnam Veterans 1974 (Washington University. Department of Psychiatry Lee I. Robbins; Special Action Office Monograph, Series A #1, April 1973)
Aggression	Stressful Life Events and Their Contexts (Rutgers University Press 1981; Barbara Snell and Bruce T. Dohrenwend)
Isolation	Young Adults Survey, New York State Drug Study (Columbia University School of Public Health. Longitudinal Research on Drug Use 1978, Denise B. Kandel
Fatigue	Young Adults Survey
Social Desirability response set	Health Insurance Study 1975-1982 (Rand Corporation; Santa Monica, CA Dec 1979 John E. Ware, Jr.)

Anxiety	Health Insurance Study
Depressive episode	Diagnostic Interview schedule (Dr. Lee Robbins, Washington University, St. Louis, MO)
Panic disorder	Diagnostic Interview Schedule

An acceptability pretest of the developed questionnaires was conducted in May 1981. Twenty study subject, 18 spouse, and 2 next-of-kin interviews were completed. Following minor modifications, these instruments became the final questionnaires for the implementation contract. They were not publicly released prior to implementation.

3. Questionnaire Implementation: Contract Award and Administration

Louis Harris and Associates, Inc (LHA) was competitively awarded a 9-month implementation contract in September 1981. The purpose of this contract was to collect baseline data on the study population through the use of the developed questionnaires. The specific elements of each questionnaire are presented in Table III-2.

Table III-2

ELEMENTS OF THE QUESTIONNAIRES

Type Questionnaire	Elements
Study Subject	Demographic, educational, occupational, medical, compliance, toxic exposures,and reproductive experience
Spouse (present and former)	Comprehensive reproductive history
Next-of-kin	Modification of study subject questionnaire
Noncompliant (Telephone)	Perception of health, use of prescribed medication, medical conditions, work absenteeism, income and reasons for noncompliance

LHA first reviewed the questionnaire and reformated the instruments from a horizontal to a longitudinal format to better suit their interviewing style. The contractor's management personnel selected interviewers, scheduled training programs, and defined procedures to be used in the conduct of the contract. Ninety interviewers were selected and trained in a series of 11 training sessions held throughout the United States and Europe. All training sessions were taught by either the LHA Vice-President for Research Services, or the Project Director. All LHA interviewers (84 women and 6 men) had a minimum of 1 year prior experience in interviewing, with at least 1 experience with health data collection. Race matching of interviewers and respondents was accomplished in the majority of cases in order to enhance rapport and accuracy of data (Hyman, 1954). Interviewer bias was additionally limited through a review of the interviewer's military experience and background. Several potential interviewers were excluded because they were spouses of USAF personnel or personally knew some of the study participants. The LHA staff was not informed of the exposure status of any individual in this study before or after the completion of the contract. LHA interviewers reported to the Project Director in the New York office on a weekly basis. The first two interviews of each interviewer were critiqued by this staff prior to allowing further interviewing. Additionally, the USAF received weekly reports from the Project Director on all aspects of the contract. An interactive relationship between the USAF and LHA staff was essential throughout this contract.

In addition to data collection, LHA also contracted to locate the study population, obtain signed medical release forms, assess the intent of the subject to participate in the physical examination phase of the morbidity study, and to attempt to convert those individuals who absolutely refused all data collection attempts.

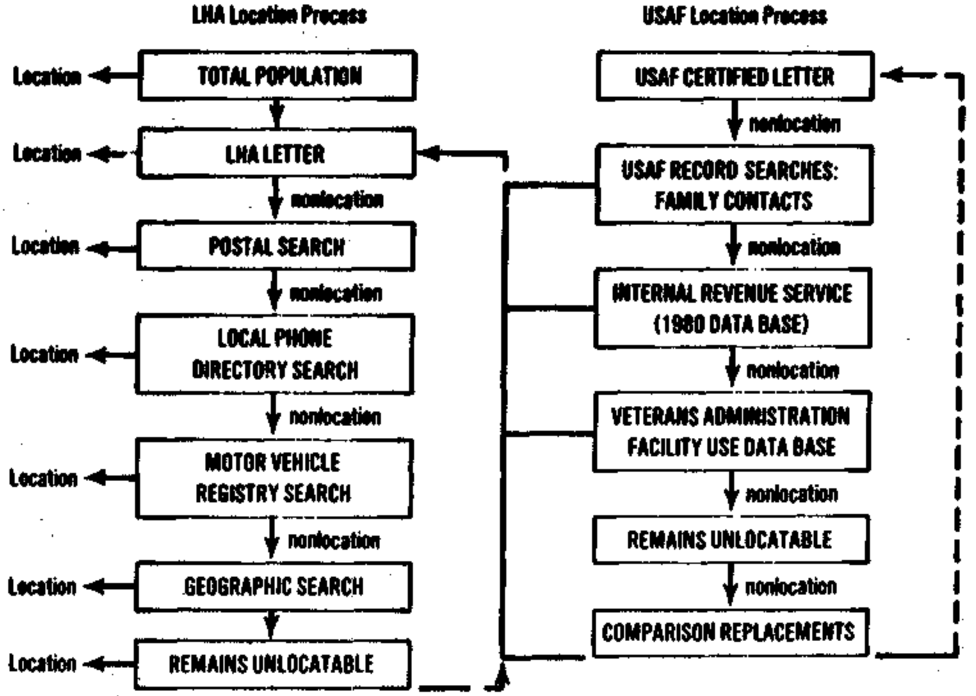
4. Questionnaire Implementation: Location

Initial contact with the Ranch Hand and the original comparison population occurred in November 1981. At this time each potential participant was sent certified introductory letters and a fact sheet. These letters were signed by the Secretary of the USAF and the USAF Surgeon General. They defined participation as voluntary and explained the limited confidentiality of positive medical findings diagnosed during the physical examination portion of the Morbidity study. Examples of these materials are presented in Appendix XI. LHA followed the USAF letters with their own introductory letters. The assigned interviewer then contacted the potential study participant by phone for scheduling the in-person questionnaire. Initial contact with the shifted population was also completed by this series of letters and telephone contact. Letter mailing and identification of this group to LHA was completed by April 1982. Initial contact with the replacement comparison group occurred by letter followed by LHA phone contact until the final questionnaire administration contract extension, i.e. November 1982. From November 1982 all initial contact with replacement comparisons was by the USAF by telephone. For this small group, questionnaire administration was scheduled by the USAF interviewers in conjunction with the physical examination. Introductory USAF letters were sent after the replacement comparison agreed to complete the physical examination. LHA letters were, of course, not sent to this population. Therefore, within the replacement subset of comparison participants there are individuals whose interview was completed by the USAF at the physical examination site and not in their home.

Table III-3 presents the algorithm developed for locating study participants during the questionnaire administration contract.

Table III-3

ALGORITHM OF THE LOCATION PROCESS OF LHA AND USAF
DURING THE QUESTIONNAIRE ADMINISTRATION CONTRACT



This algorithm demonstrates the multiple sources used to locate study participants. This process was completed for all study subjects forwarded to LHA (Ranch Hand; original, shifted, and replacement comparisons). For a small number of replacement comparisons (23) not forwarded to LHA because of contract termination, the majority of the USAF location process was completed while the LHA process was not completed. Replacements for the original and shifted nonlocatable comparisons were not identified to LHA until the location algorithm was complete.

5. Questionnaire Implementation: Data Collection

Once the study participant was located, an individual LHA interviewer was assigned. The interviewer initially contacted the participants by phone or by telegram if his phone number was unlisted. The participant was informed of the length of the interview (average 1.5 hrs; range 30 minutes to 3 hours) and scheduled the in-home questionnaire at his convenience. Whenever possible, interviews of current spouse were scheduled for the same day and followed the study participants interview. These interviews were conducted privately in order to obtain independent reproductive histories. If the participant refused to participate in the interview, his name was forwarded to the central office and conversion attempts were made by the LHA central office. Noncompliant telephone questionnaires were administered to the refusals by the central office. The telephone administration system was implemented in April 1981.

At the time of the in-person questionnaire, all participants read and signed a privacy act statement and completed a Life Events Chart. This chart acted as a recall guide to the chronology of events discussed in the questionnaire. Interviewers were required to ask questions exactly as written, were not allowed to interpret questions, or inject personal commentary, nor were they allowed to skip between sections of the questionnaire. They were also instructed to probe "don't know" answers at least once. At the conclusion of the interview, medical record release forms were signed for those physicians and medical facilities reported in the questionnaire, and the study participant was also asked whether or not he would agree to participate in a physical examination. The respondent was also asked to give the current name and address for each former spouse listed in the questionnaire, so that spouse interviews could be scheduled and conducted with these individuals. Medical permission forms for medical record data of spouses and children were inadvertently omitted at the time of interview. A system to obtain these data was initiated following the USAF receipt of questionnaires.

Due to high and favorable participation rates, patient flow and logistic difficulties in both the questionnaire and physical examination portions of the morbidity study, it was necessary to extend the LHA contract through November 1982 and the examination contract to 15 December 1982. Because the contracts did not overlap experienced USAF interviewers were required to complete questionnaire administration to participants at the physical examination site.

6. Questionnaire Implementation: Data Processing

All completed interviews were sent to the LHA central office following initial field editing by the responsible interviewer. Each completed questionnaire was repeatedly edited by the LHA Project Director's staff. To ensure that every question was answered, participants were recontacted to provide missing data. This staff also coordinated and supervised the coding, keypunching and key verification of all completed interviews as they were translated to computer tape. Classifications and coding schemes used included the International Classification of Diseases, 9th Revision, Bureau of Labor Statistics, Standard Industrial Classification, and specific USAF codes for job and aircraft designation. LHA reported that it took an average of 2 hours to fully edit and code each interview. All keypunching was 100% verified. Discrepancies were reconciled by review of the hard copy interview. A set of data cleaning programs was developed by the LHA data processing staff to locate and identify errors and inconsistencies in the data set on tape. These programs were reviewed and approved by USAF data processing personnel. In addition, the USAF developed additional programs to further cleanse the data. In neither case were programs used that would force data to meet inner consistency checks. The objective of data editing was to ensure that the final data set accurately represented the respondent's information. A total of 6 data tapes were delivered to the USAF from LHA. A copy of the data tapes was sent directly from LHA to the Advisory Committee on Special Studies Relating to the Possible Long-term Health Effects of Phenoxy Herbicides and Contaminants. The data tapes were delivered at least 3 months later than the original contract established dates.

7. USAF Data Processing

The questionnaire data collected during contract extensions and at the physical examination site were edited but not keypunched. These data were delivered in hard copy to the USAF. The USAF coded, verified, keypunched and entered the data on computer tape. Because of late data delivery and the volume of unkeypunched data, systematic review and comparison of all (LHA and USAF) hard copy questionnaires to the data tapes was not accomplished as planned. A comparison of 25 hard-copy questionnaires to data entered on the tapes was accomplished by USAF data processing personnel. The findings of this keypunch review are presented in Chapter VI, Quality Control Procedures. Morbidity coding was reviewed; however, because of incorrect and missing morbidity codes the USAF recoded all reported medical conditions. Additionally, the LHA data tapes did not include all data collected by the interviewer in the supplemental recording book. These data were required to form the link between the parents, their children, and all medical provider data (the basis of medical verification procedures). The USAF therefore developed systems and hired personnel to support the entry of these data in preparation for analyses.

8. Summary

Questionnaire methodology includes the development and implementation of multiple questionnaire instruments through civilian contractors. The NORC developed and LHA administered the instruments. Both contractors worked closely with the USAF. These close interactions resulted in the participation shown in Table III-4.

Table III-4

SUMMARY OF QUESTIONNAIRE PARTICIPATION

Type Questionnaire	Ranch Hand	Counts of Participants: Comparison — Original	Shifted	Replaced	Air Force	TOTAL
- Study Subject	1174	956	200	346	30	1532
- Spouse (Current & Former)	1208	962	200	333	5	1500
- Telephone Noncompliant	10	34	8	7	20	69

Medical record release forms were obtained by the contractor during data collection. These permission forms are the basis of the medical record verification program presently in process for data collected by questionnaire. Data delivery to the USAF from the contractor was delayed. Medical coding was reaccomplished and data linkage systems were developed by the USAF to make the most efficient use of the data collected.

Chapter IV

PHYSICAL EXAMINATION METHODOLOGY

Subsequent to the administration of the questionnaire, a voluntary comprehensive physical examination was offered to all individuals in both the exposed and comparison groups. The primary prerequisite for entry into the examination phase of the study was the completion of the baseline questionnaire. In the event that the initially selected comparison chose not to participate in both the questionnaire and the physical examination, a replacement was selected from among the other comparisons in the matched set, as depicted in Chapter II, Figure II-1. The two and one-half day examination was conducted in Houston, Texas by the Kelsey-Seybold Clinic, P.A. At the time of evaluation, an extensive physical examination, medical history with a review of systems, and indepth laboratory analyses were conducted. A concise Examiner's Handbook in the Air Force Health Study Protocol placed strong emphasis on quality assurance and was used to minimize variability and insure comparability of data over the 12-month duration of the physical examination contract. Strict compliance with this document was required. Physical examinations were performed at the earliest practical time following the completion of the questionnaire, since close sequencing would limit the development of major symptoms or diseases in the interval between the questionnaire and the examination.

Physical examinations were performed at a single location and all contractor personnel evaluated the participants without knowledge of their exposure status. The number of examiners and the turnover of staff members was kept to a minimum to limit between-examiner variability. A more detailed discussion of the physical examination quality control program is contained in Chapter VI.

All laboratory tests were subjected to rigid quality control, and laboratory and physical examination data were measured on a continuous scale whenever possible to improve statistical power in the analysis. An Air Force physician was present at the examination site throughout the duration of the contract to act as a liaison between the subjects, the contractor and the Air Force, and to insure that the examination protocol was scrupulously followed. Although the on-site monitors closely observed each examiner and technician, the monitors remained unobtrusive during the examinations, and were not permitted to confirm, criticize or otherwise influence the examiners' findings.

The components of the physical examination were specifically selected to address those medical end points known or suspected to be caused by phenoxy herbicides and dioxin (Crow, 1970; Kimbrough, 1980). The question of whether significant chronic effects are produced in humans is a controversial issue (Homberger et al, 1979; Reggiani, 1980; Wolfe and Lathrop, 1983). Reviews of physical chemistry data, animal toxicity data, human exposure case reports, and epidemiologic studies have been relatively unsuccessful in identifying specific and objective medical end points for the chronic effects of exposure (Jirasek et al, 1973; Jirasek et al, 1974; Poland, 1979; Young, 1978). The list of known or suspected acute and subacute effects following TCDD exposure is extensive, and many of the end points are highly subjective and extremely difficult to evaluate (Oliver, 1975; Poland et al, 1979). While chloracne appears to be a consistent, chronic effect of moderate to heavy exposure, the implication of this condition on long-term health is unknown (Young et al, 1978). At best, a list of potential organ systems which should be carefully evaluated can be developed.

Ideally, one would like to have a sensitive and specific examination or laboratory procedure to detect the effects of these chemicals in human tissues. Unfortunately, there is a lack of clearly defined end points in the scientific literature, and, other than chloracne, distinct clinical syndromes or unique effects indicative of chronic illness have not been identified. The signs and symptoms currently attributed to exposure are confounded by age and other causes, and the effect, if present, may be lost in common symptoms from other causes of disease (in contrast to conditions such as diethyl-stilbestrol-induced vaginal adeno-carcinoma and angiosarcoma of the liver caused by vinyl chloride exposure). In the absence of sensitive and specific indicators of exposure, a comprehensive examination format was developed around these target organ systems listed in Table IV-1. The complexity and the length of the evaluation and the invasiveness of each examination procedure were all key factors in the final choice of the examination components since all of these factors have a significant impact on the compliance behavior of the individuals considering participation in the study.

Table IV-1

TARGET ORGAN SYSTEMS/CONDITIONS

Dermatologic

Hepatic

Neoplastic

Neurological/Psychiatric

Endocrine/Reproductive

Immunologic

Hemopoietic

A general summary of the major components of the examination is presented in Table IV-2, and examples of the examination forms are included in Appendix VI. The laboratory procedures conducted on each subject are listed in Table IV-3. For each participant 20 cc of serum, 100 cc of urine, and all remaining semen were aliquoted and stored at -70°C for future analyses. When technology developments identify additional analytic procedures which will assess the health effects of phenoxy herbicides and dioxin, these specimens will then be tested. The slides used in the 10,000 white blood cell differential and the semen analysis were also preserved.

Table IV-2

RANCH HAND II
PHYSICAL EXAMINATION

General Physical Examination	(Internist)
Neurological Examination	(Neurologist)
Dermatological Examination	(Dermatologist)
Electrocardiogram	(Resting, 4-Hour Fasting)
Pulmonary Function Study	(1 Second Forced Expiratory Volume, Vital Capacity)
Chest X-ray	
Nerve Conduction Velocities	(Ulnar, Peroneal, Sural)
Psychological Evaluation	
Minnesota Multiphasic Personality Inventory (MMPI)	
Cornell	
Wechsler Memory Scale I	
Wechsler Adult Intelligence Scale (WAIS)	
Wide Range Achievement Test (WRAT)	
Halstead-Reitan Neuropsychological Battery	
Patient Outbriefing and Discussion of Individual Results	(Internist) (PhD Psychologist)

Table IV-3

LABORATORY PROCEDURES

Chemistry Panel:	
Blood Urea Nitrogen (BUN)	Serum Glutamic Oxaloacetic Transaminase (SGOT)
Creatinine	Serum Glutamic Pyruvic Transaminase (SGPT)
Cholesterol	Gamma Glutyrl Transpeptidase (GGTP)
High-Density Lipoprotein	
Triglyceride	Lactic Dehydrogenase (LDH)
	Creatine Phosphokinase (CPK)
	Blood Alcohol
Total Bilirubin	
Direct Bilirubin	
Alkaline Phosphatase	
Glucose } Fasting and 2 Hour	
Cortisol } Fasting and 2 Hour	
Hormone Assay:	
Leutenizing Hormone (LH)	Triiodothyronine (T3)
Follicle Stimulating Hormone (FSH)	Total Thyroxine (T4)
Testosterone	Free Thyroxine Index (FTI)
Hematology Panel:	
Erythrocyte Sedimentation Rate	
Prothrombin Time	
Serological Test for Syphilis (RPR)	
White Blood Cell Count (with 10,000 cell differential)	
Red Blood Cell Count	
Hemoglobin	
Hematocrit	
Red Cell Indices	
Platelet Count	
Urinalysis	
24-Hour Urine:	
Volume	
Delta Amino Levulinic Acid	
Coproporphyrins	
Uroporphyrins	
Porphobilinogen	
Creatinine	
Semen Analysis:	
Volume	
Count	
Abnormal Forms	
Hepatitis B Testing:	
Surface Antigen	
Antibody to Surface Antigen	
Core Antibody	

Under special circumstances, additional laboratory procedures were carried out on selected participants. Those individuals with a history of having fathered children with birth defects had blood drawn for a determination of karyotype. The serum of participants with a medical history or review of systems indicating the possibility of an immune system deficiency was evaluated by immunoelectrophoresis. Antinuclear antibody determinations were performed on individuals with a history suggestive of connective tissue disorders. In addition, all individuals with a past history of hepatitis were tested for antibody to hepatitis A virus.

After 20 April 1982, all participants whose study identification number ended in either 1, 3, 6 or 9 were selected for special immunologic testing. Blood from these individuals was drawn and sent to a subcontractor for the evaluation of B and T cell counts, enumeration of T cell subpopulations, and studies of B and T cell function following mitogen stimulation. In all, 592 randomly selected subjects took part in this portion of the evaluation.

Since human sensitivity and compassion could seriously enhance participation in the follow-up phases of the study, every opportunity was taken by the contractor and the Air Force to make the experience enjoyable, relaxing and rapport building. Study participants were housed in a comfortable motel, and transportation, meals and a modest stipend were provided. Family members were encouraged to accompany the participants, but at no expense to the government. Any emergency medical care required by the participants during their stay in Houston was provided by the contractor and paid for by USAF. Additionally, any diagnostic procedures necessary to clarify potentially life-threatening conditions were also performed (computerized tomography, cardiology consultation, etc.). Detailed in-briefings were provided to all participants (and optionally to accompanying family members), in order to explain the background and nature of the study as well as the routine medical requirements for the fasting status laboratory procedures. During waiting periods between examination phases, participants were encouraged to become acquainted with other participants and ask any questions they had about the examination, its rationale or the Air Force Health Study. The normal tension associated with psychological testing was relieved by frequent breaks. Any individual problems were quietly and diplomatically managed by the contracting staff and the site monitor. Over 95% of the participants expressed praise for the quality and thoroughness of the examination and pledged to return to the next examination.

Subjects arrived in Houston on either a Sunday or a Tuesday afternoon. A 1-hour briefing was given to each group of participants by the Air Force monitor and a Kelsey-Seybold physician. During this briefing, the purpose of the study and a detailed explanation of the examination content and schedule were discussed. The next 2 days (Monday/Tuesday or Wednesday/Thursday) were spent in the examination. Upon arrival at the clinic on the first morning, all participants were met by two Kelsey-Seybold staff members: the Patient Coordinator and the Program Director. After the day's events were explained, medical history and other forms were completed and blood specimens were drawn. All participants on active flying status with the Department of Defense or FAA had their blood drawn while reclining. Others had the option of sitting or lying.

All fasting blood specimens were obtained following a minimum of seven hours without alcohol, food or cigarettes. Participants were requested to consume a 250-gram carbohydrate diet for the 3 days prior to their arrival to prepare for the fasting and 2-hour postprandial glucose testing. All alcoholic beverages were to be avoided as well. Compliance with these requirements and the 24 hour urine collection was determined. Breakfast followed the blood draw and postprandial specimens were then obtained at appropriate times. One-half of each group underwent physical examination on the first day while the other half were in psychological testing. On the second day, the schedule was reversed. During the final half-day, each participant received detailed briefings from a PhD psychologist and one of two Internal Medicine specialists. During these briefings, the results of all portions of the physical examination performed at the Kelsey-Seybold Clinic were discussed with the subject, any questions he had were answered, and suggestions for medical treatment or follow-up were made when indicated. If immediate follow-up was indicated, direct contact with the participant's personal physician was made, and appropriate treatment was arranged. The results of those laboratory procedures performed at subcontracting laboratories and the results of the MMPI were not discussed. Payment of expense vouchers and the provision stipend checks were delayed until after the completion of the debriefing to encourage attendance at these sessions.

Chapter V

STUDY SELECTION AND PARTICIPATION BIAS

1. Introduction

The main emphasis in the design and conduct of any epidemiologic study is comparability of the groups under study (Monson, 1980), and the strength of epidemiologic inference is directly associated with group comparability. In this study, Ranch Hand and comparison group comparability was assured by design since strict criteria were used to define the exposed (Ranch Hand) and the nonexposed (comparison) cohorts and since replacement comparisons were to be matched to original comparisons by perception of health. The cohorts were matched on the variables of age, race, and occupation group to minimize confounding and assure comparability in these variables. Within the nonexposed cohort, however, 4 subgroups resulted from the original match, the removal of ineligibles, replacement for noncompliance, the termination of the questionnaire and physical examination contracts, and the lack of data to match replacements to original comparisons. These groups are: original comparisons (O), shifted comparisons (S), replacement comparisons (R), and those replacement comparisons questioned by experienced Air Force interviewers (A). Because of logistic limitations, scheduling opportunities differed somewhat for each of these groups. Since compliance with this study was voluntary, the occurrence of differing scheduling options could have resulted in inadvertent selection bias (Cook and Campbell, 1979). The purpose of this chapter is to present the factors known to influence study participation, describe and analyze the responses of the Ranch Hand and the comparison groups to the opportunity to participate and to assess the potential bias of differential compliance. The analytic, and inferential implications of self-selection and potential participation bias will also be discussed. Participation is described in terms of location and compliance. A total of 1208 Ranch Hands and 1669 comparisons were the potential participants in this morbidity study.

2. Factors Known to Influence Study Participation

The study protocol estimated that 65% of the Ranch Handers would participate in the questionnaire and that 60% of these subjects would also participate in the physical examination. One major reason for these low estimates was the recognition of the negative influence of employment in flying occupations on compliance to physical examination. This negative influence was reinforced in the press and the subsequent advice of the Airline Pilots Association to their members not to participate in this study. This difficulty was anticipated by the principal investigators and is discussed in section VIII of the study protocol. Table V-1 presents a list of factors that could affect study participation. Those components of each factor that are considered in the study protocol for data collection are identified with an asterisk.

Table V-1

FACTORS POTENTIALLY AFFECTING STUDY PARTICIPATION

Factors	Components
Health Bias	*Self perception Current Use Long Term Care Abortion Pattern *Absenteeism *Current Medications Fertility History Current Family Health Familial History Severity of Past Disease Pending Retirement Bias Death
Logistic Factors	*Time Away From Family *Time Away From Job Distance to Exam Site *Income *Active Pilot (FAA)
Other Factors	Flying Status (USAF) Officer/Enlisted Age Race Current Status: AD/Sep Stipend Employment Status Dissatisfaction with Military
"Operational Factors"	Manner of Study Contact Scheduling Window Interviewer Bias
Publicity Bias	Motivational Bias Compensation Bias

The factors and the outlined components of each factor suggest the complexity of the compliance/noncompliance decision made by each study participant, Ranch Hander or comparison. The importance assigned to each component by the individuals in the Ranch Hand and comparison groups is most likely not equivalent. The Ranch Hand group was actively encouraged by the Ranch Hand Association to participate while no such organization exists for the comparison group.

3. Location

Mailing addresses for each study subject were determined through multiple military and civilian sources. Study subject location was initially identified by a certified mailing to these addresses. Current mailing addresses could not be identified for the nonlocatable population. Two-tenths percent of the Ranch Hand and 0.5% of the total comparison group were nonlocatable. This is well above the 99% location rate estimated in the study protocol. Table V-2 presents the counts of the located/nonlocated population by Ranch Hand and type of comparison.

Table V-2

COUNTS AND PERCENT OF LOCATABLE/NON-LOCATABLE
ALIVE STUDY SUBJECTS BY RANCH HAND AND
NATURE OF THE COMPARISON GROUP

	Ranch Hand	Comparison: Original	Comparison: Shifted	Comparison: Replacements*	Comparison: Total
Locate	1206 (99.8%)	1023 (99.7%)	212 (100%)	425 (98.6%)	1660 (99.5%)
NonLocate	2 (0.2%)	3 (0.3%)	-	6 (1.4%)	9 (0.5%)
	1208	1026	212	431	1669

*Includes those individuals interviewed by USAF interviewers (A).

The two unlocated Ranch Hand individuals were separated from the military, and both had been nonflying enlisted personnel when on active duty. One was Black and the other was non-Black. Three of the 9 unlocatable comparisons were in the originally selected cohort. These 3 individuals were separated from the military, enlisted when on active duty (1 was a flying enlisted while the other 2 were nonflying enlisted) and all were non-Black. The locate algorithm was not completed on the replaced comparison "cannot-locate" population. Five of these 6 individuals were non-Black. The Black individual was separated and had served in an enlisted nonflying capacity. One other separated nonflying enlisted individual was non-Black. The remaining 4 replaced nonlocated comparisons were non-Black pilots. Two of these were separated, 1 was on reserve status and the other was retired. Overall, nonlocation did not impact data collection in this study. The 11 nonlocatable subjects are assumed to be alive and location will be attempted for the follow-up phases of the study. The replacement comparison group nonlocatable rate of 1.4% is of borderline significance when contrasted with the rate in the originally selected group (P = 0.06). This test was performed on the proportions using the normal approximation to the binominal. This difference was a result of the termination of the questionnaire contract prior to completion of the examination process. The names of 3 of the 6 replacement individuals were not sent to the questionnaire contractor while the 3 others were sent only 1 month prior to contract termination. The replacement strategy as designed in the study protocol could not be implemented due to termination of the questionnaire contract prior to the completion of the physical examination contract.

4. Study Participation: Compliance

Study participation was characterized as being either fully compliant (FC) (completed the physical examination and the questionnaire); partially compliant (PC) (completed only the questionnaire) or noncompliant (NC) (refused the physical examination and the in-home questionnaire). Within the noncompliant group are those who completed an abbreviated telephone questionnaire. Figure V-1 shows that of the 1206 locatable Ranch Handers alive at the initiation of the morbidity study, 1045 were fully compliant to the physical examination and an additional 129 completed the questionnaire but refused the physical examination. Ten of the 32 noncompliant Ranch Handers completed the telephone questionnaire.

Figure V-1
RANCH HAND PARTICIPATION

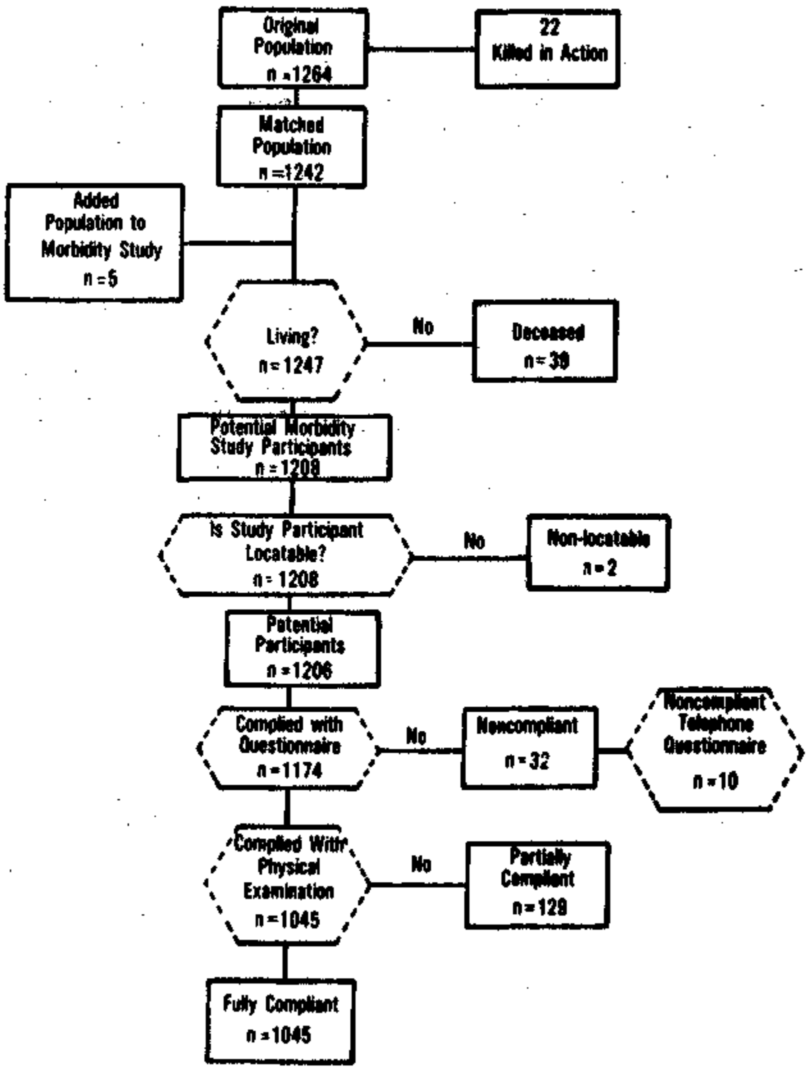
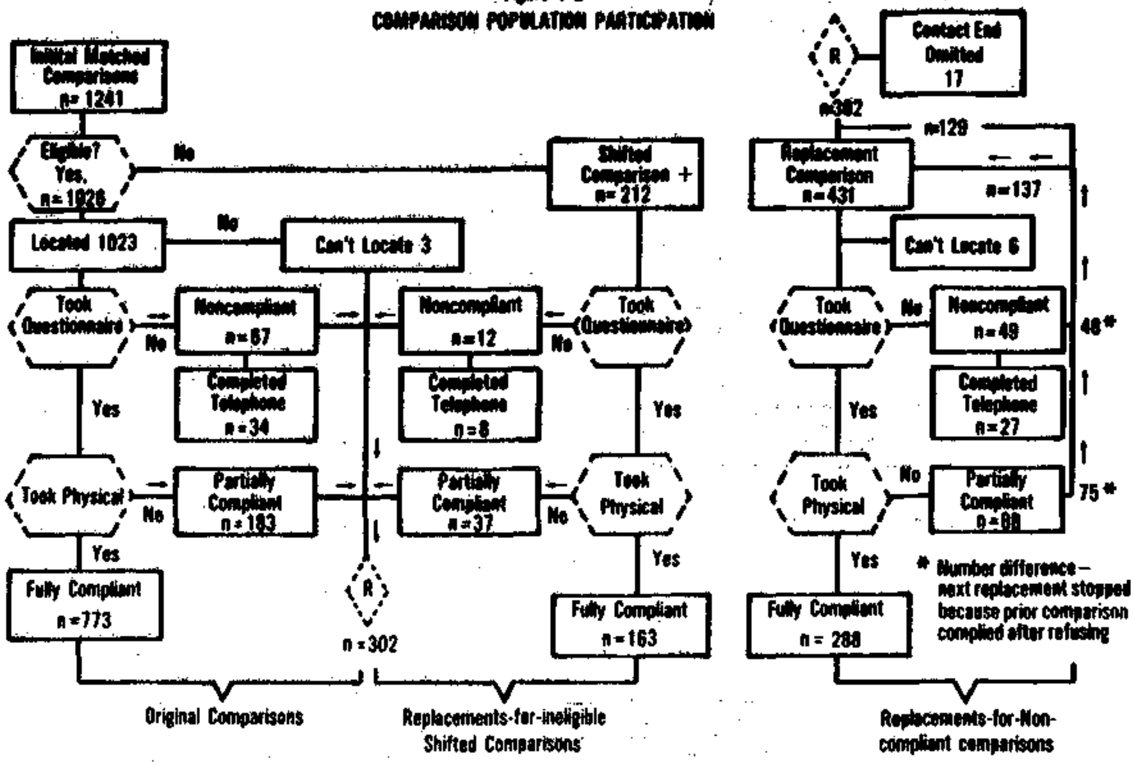


Figure V-2 describes the compliance patterns for the original, shifted and replaced comparison population. Of the 1023 locatable eligible original comparisons, 773 were fully compliant, 183 were partially compliant and 67 were noncompliant. Thirty-four of the noncompliant individuals completed the short telephone questionnaire.

Figure V-2
COMPARISON POPULATION PARTICIPATION



Data collected by the noncompliant telephone instrument was delivered to the United States Air Force in written format following the implementation of the replacement strategy. The telephone questionnaire was not administered to the noncompliant replacement candidates prior to selection for the study, and therefore, the data necessary to match the original and replacement comparisons by similar perception of health status was not available (Lathrop, 1982). The next living individuals in the designated matched sets were selected as replacements. The data collected in the noncompliant instrument will be discussed in future publications.

Figures V-1 and V-2 are summarized in Table V-3, in which Ranch Hand and comparison participation is presented.

Table V-3

FULL, PARTIAL, NONCOMPLIANCE OF THE RANCH HAND AND COMPARISON POPULATION BY NATURE OF THE COMPARISON GROUP, i.e., ORIGINAL (O), SHIFTED (S), REPLACED (R), AIR FORCE INTERVIEWERS (A)

		Comparisons				
	RH	O	S	R	A	Total
Fully Compliant (FC)	1045*	773	163	258	30	1224
Partially Compliant (PC)	129	183	37	88	-	308
NonCompliant (NC)	32	67	12	49	-	128
TOTALS	1206	1023	212**	395	30	1660

*4 individuals were interviewed at the Physical Examination site by USAF interviewers.

**3 Additional shifted comparisons were removed due to ineligibility identified following data collection.

The mean age of the population by compliance group is presented in Table V-4.

Table V-4

MEAN AGE OF THE RANCH HAND AND COMPARISON POPULATION BY NATURE OF THE COMPARISON GROUP (O, S, R) AND TYPE OF COMPLIANCE (NC, PC, FC)

Type Compliance	Ranch Hand Mean Age	Comparison Mean Age O	S	R*
Non-Black				
NC	41	41	39	40
PC	43	42	39	41
FC	44	45	43	41
Black				
NC	39	39	35	34
PC	39	43	39	38
FC	41	42	42	40

*Includes those individuals interviewed by USAF interviewers (A).

Table V-4 indicates that the noncompliant group is on the average younger than either the partially or fully compliant in both Black and non-Black strata. The compliant population is further described by race in Table V-5. This data is abstracted from Appendix XII, Occupational Category and Race of the Fully Compliant Population in Percent and Counts.

Table V-5

PERCENT FULLY COMPLIANT OFFICER/ENLISTED CATEGORIES BY RACE RANCH HAND AND COMPARISONS (O, S, R)

	Ranch Hand	Comparison Original	Shifted	Replacements
Non-Black				
Officers	85%	73%	78%	61%
Enlisted	88%	77%	77%	74%
Black				
Officers	67%	88%	*	*
Enlisted	90%	75%	69%	62%

* No individuals in this category.

This table suggests that Ranch Hand enlisted personnel complied at higher rates than officers and that Ranch Hand non-Black officers complied more than Black officers. The number of Black participants is very small and is therefore not included in the following analyses but is included in Appendix XII.

Appendix XVII was used to construct the data in Table V-6. Flying status is presented as flying/nonflying which includes both military and civilian information. Military status is categorized as active duty, retired, and separated/reserve.

Table V-6

PERCENT FULLY COMPLIANT OFFICERS BY FLYING STATUS AND MILITARY CATEGORY (NON-BLACK ONLY)

	Ranch Hand n=372		Comparison: Original n=283		Comparison: Shifted n=46		Comparison: Replacements n=113	
	Flying	Non-Flying	Flying	Non-Flying	Flying	Non-Flying	Flying	Non-Flying
Active Duty (A)	77.8	96.3	58.9	76.2	87.5	75.0	57.9	88.9
Retired (R)	86.0	93.5	86.0	86.5	100.0	96.0	83.3	77.1
Separated/ Reserve (SV)	51.9	87.0	39.3	62.9	37.5	61.5	32.4	63.0

The flying separated/reserve category in this data set complied less than any other strata ($P<0.01$), and flying status contributed significantly to the compliance decision ($P<0.01$).

As illustrated in Table V-6, a complex set of interactions was involved in compliance. A log-linear model which was fitted to the three-way frequency table based on flying/military status, compliance, and group membership, revealed a three-way interaction ($P=.07$) in these data, rendering interpretations based on simpler models misleading. Since age and race are also related to flying/military status, tests of association between these factors and compliance need to be studied in the context of the many interactions present. These more complex relationships will be explored in future reports.

A summary of compliance is presented in Table V-7.

Table V-7

PERCENT OF THE STUDY POPULATION COMPLYING TO THE QUESTIONNAIRE AND PHYSICAL EXAMINATION

	Ranch Hand	Comparison		
		Original	Shifted	Replacements
Questionnaire	97% (1174/1206)	92% (956/1023)	94% (200/212)	88% (376/425)
Physical Examination	87% (1045/1206)	76% (773/1023)	77% (163/212)	68% (288/425)

Ranch Hand personnel participated in the questionnaire at a rate higher than all comparison groups. This participation was 32% greater than the original protocol estimate of Ranch Hand compliance. Differential compliance to questionnaire did occur in the comparison groups with the original and shifted group complying 5% more than the replaced comparison group (unadjusted; P=0.003). Table V-7 shows that differential compliance also occurred between the Ranch Hand and the original comparison group in their compliance to physical examination (unadjusted; P<0.001) as well as within the comparison groups with the original and shifted comparison groups complying 8-9% more than the replaced group (unadjusted; P<0.001).

5. Noncompliance

The reasons given by study participants for noncompliance were compared. Appendixes XIII and XIV display all reasons given. These data were collected in a nonstandard manner by Louis Harris and Associates, the Kelsey-Seybold Clinic, and USAF personnel. The responses were then allocated to the categories presented in the appendix. They describe that the majority of the reasons given for noncompliance were "no time-no interest" and passive refusal. Table V-8 shows the percent of refusals in the Ranch Hand and comparison groups implying these disinterest reasons.

Table V-8

PERCENT OF REFUSALS CATEGORIZED AS REFUSALS FOR REASONS OF DISINTEREST

	Ranch Hand	Comparison Original	Comparison Shifted	Comparison Replacements
Questionnaire	86%	67%	91%	49%
Physical Examination	50%	58%	54%	58%

These data indicate that the noncompliant replacement comparisons were passive refusals less often than were the other comparison groups. The percent refusals due to job commitment and confidentiality are described in Table V-9.

Table V-9

PERCENT OF QUESTIONNAIRE REFUSALS CATEGORIZED AS
JOB COMMITMENT AND CONFIDENTIALITY

	Ranch Hand	Comparison Original	Comparison Shifted	Comparison Replacements
Job Commitment	-	3%	-	24%
Confidentiality/ Active Duty	5%	14%	-	24%
TOTAL	5%	17%	-	48%

Forty-eight percent of the replaced population stated that they refused to participate in the questionnaire because of a job commitment or the issue of confidentiality.

6. Scheduling Opportunity

The names of the Ranch Hand and original comparison groups were provided to the questionnaire contractor in November 1981. The contractor was given the shifted comparison population in April 1982 and the replacement population continued to be identified to the contractor through 15 Nov 1982. Physical examination scheduling was contingent upon completion of the questionnaire. Therefore, while the Ranch Handers and the original comparisons had 1 year to schedule and complete the study, the shifted comparisons had a maximum of 9 months, and the replacement comparisons were afforded a more limited scheduling opportunity.

Figure V-3

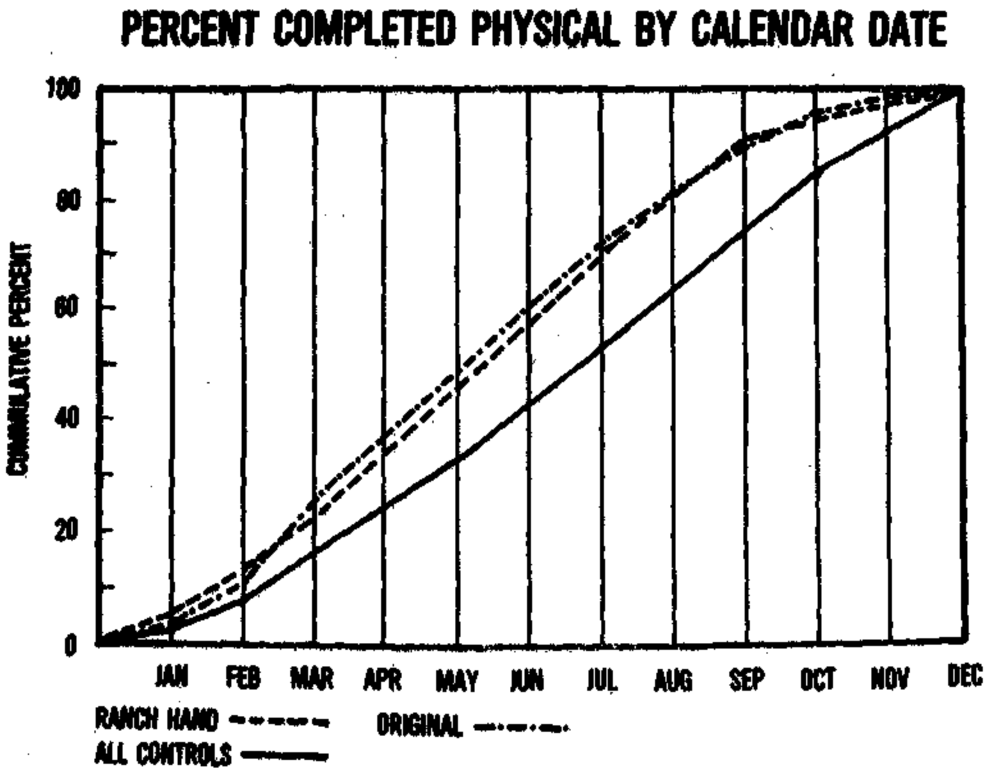
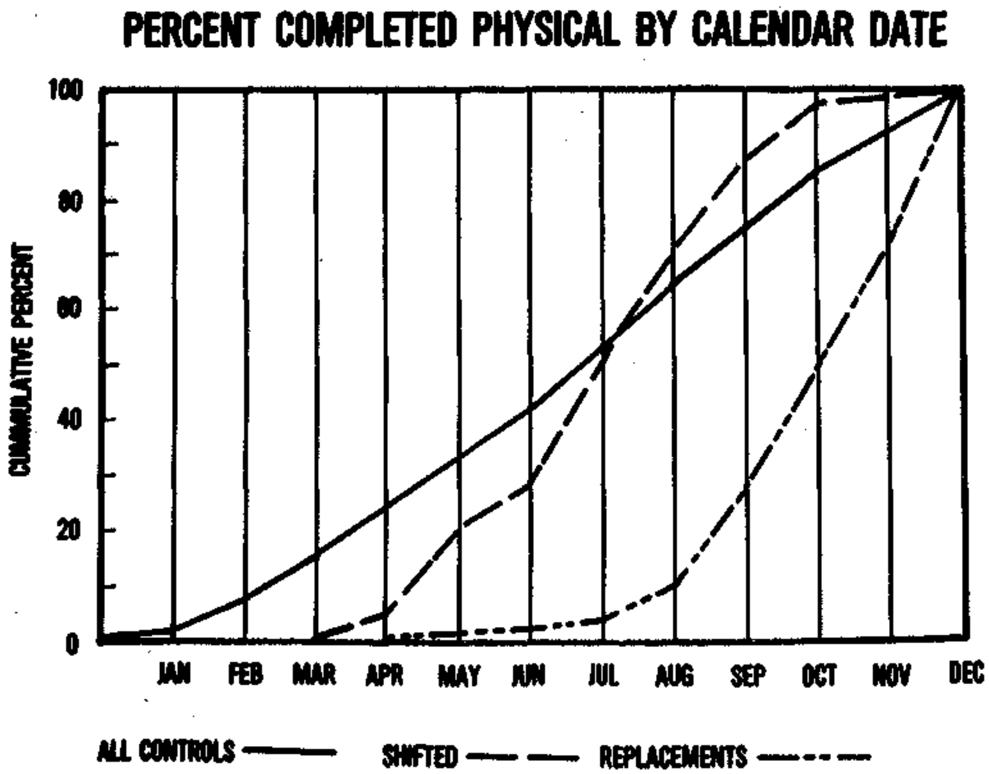

PERCENT COMPLETED PHYSICAL BY CALENDAR DATE
COMMULATIVE PERCENT
100
80
60
40
20
0
JAN
FEB
MAR
APR
MAY
JUN
JUL
AUG
SEP
OCT
NOV
DEC
RANCH HAND
ORIGINAL
ALL CONTROLS

Figure V-4



Figures V-3 and V-4 show the cumulative percent of the Ranch Hand and comparison groups (original, shifted and replacement) completing the physical examination by time. Figure V-3 shows the similar time pattern of the Ranch Hand and original comparison group completing the physical examination. Figure V-4 shows that the shifted and replacement comparison groups were restricted in scheduling by the nature of the implementation of the design and contract time limitations. The overall comparison group cumulative completion of physical examination by calendar date is shown on both Figure V-3 and V-4. Fifty percent of the Ranch Hands and the original comparisons had completed their physical in May 1982, 50% of the shifted group had completed in July 1982, while 50% of the replaced group did not complete until October 1982.

7. Bias Assessment of Replacement Comparisons

From the above discussions and that in Chapters II and III, 2 questions are forthcoming which are of interest to inferential reliability. First, "Are the shifted and replaced comparisons valid for use without special statistical treatment?" Secondly, "What is the bias, if any, associated with the differential compliance to the physical examination?" The following sections deal with these 2 questions in turn.

8. Evaluation of the Replacement Comparison Participants.

Since the replacements used in the study, whether S, R or A, were simply the next individual in the randomized match set involved, the appropriate test for replacement bias is the test for O, S, R or A group differences while conditioning on the variables of age, occupation and race. Specifically, if S, R and A are unbiased groups they should appear to be random samples drawn from the same population as yielded the original (O) set, after adjustment for matching variables.

Tests of replacements against original comparisons were accomplished in accordance with procedures set out in the Study Protocol. Following the protocol, replacements for comparisons were tested first in terms of 3 primary variables to be ascertained on all participants: (a) subjective health assessment, (b) current utilization of long-term health care, and (c) recent work absenteeism pattern.

Statistical testing of these 3 primary variables and of additional questionnaire and physical examination variables was done in a prespecified manner. First, group A was tested against group R to determine if these groups could be combined. If R and A could be combined, the R + A group was tested against group S to determine if these groups could be combined. If R + A and S groups could be combined, O was tested against R + A + S. All testing was done at the 0.05 level. If the test for combination was not met at any stage, appropriate subtesting was performed. When the dependent variable was categorical, testing was performed with log-linear models adjusting by occupational category and age, with age dichotomized as less than 40 years and greater than or equal to 40 years providing groups of roughly equal sizes across occupational categories. When the dependent variable was continuous, analysis was performed with a general linear models program adjusting for occupational category and age as with the log-linear models. All of this testing was done to ascertain whether the S, R and A groups could be viewed as drawn from the same population as yielded the O group. Thus, the problem is one of hypothesis testing. Careful estimation of the magnitude or directionality of effects noted was not attempted. However, the reader can evaluate magnitude by reviewing data presented in the following paragraphs.

In reporting their health status, participants were allowed to use the categories: "excellent," "good," "fair" and "poor." Because of small sample sizes, the "fair" and "poor" responses were combined in the analysis of the data. Table V-10 provides a view of the data, collapsed across occupational categories and age. No statistically significant differences between the S, R and A groups were found in either the partially compliant or fully compliant groups. However, when taken together, the fully compliant S, R and A groups appeared statistically different from the fully compliant original comparisons ($P < 0.001$). Additionally, the fully compliant O and S groups were found to be statistically different ($P = 0.01$), as were the fully compliant O and R groups ($P = 0.0045$). No statistically significant differences were noted among those individuals who took the questionnaire only.

Table V-10

SELF-ASSESSMENT OF HEALTH STATUS
(NON-BLACK PARTICIPANTS ONLY)

	Participants Who Took Questionnaire Only				Participants Who Took Questionnaire & Physical Examination			
Status → Group ↓	Excellent	Good	Fair or Poor	N	Excellent	Good	Fair or Poor	N
O	50.9%	34.7%	14.5%	173	38.0%	48.0%	14.0%	727
S	61.8%	26.5%	11.8%	34	36.4%	40.3%	23.4%	154
R	51.3%	38.2%	10.5%	76	49.6%	34.3%	16.1%	242
A	-	-	-	0	46.7%	43.3%	10.0%	30
Ranch Hand	52.5%	36.4%	11.0%	118	38.4%	41.4%	20.2%	976

O = Original Comparison
S = Shifted Comparison
R = Replacement Comparison
A = Air Force Interviewed Comparison

Use of long-term health care was assessed by inquiring about regular use of medications for heart, kidney, thyroid, renal and other disease states. No statistically significant differences were found between the O, S, R and A groups regarding regular use of medications. Table V-11 provides a view of the data collapsed across occupational categories and age.

Table V-11

MEDICATION USE
(NON-BLACK PARTICIPANTS ONLY)

Group	Participants Who Took Questionnaire Only (PC)		Participants Who Took Questionnaire and Physical Examination (FC)	
	Percent with Chronic Medication Use	N	Percent with Chronic Medication Use	N
O	23.6%	174	28.3%	728
S	14.7%	34	27.9%	154
R	19.7%	76	30.2%	242
A	-	0	16.7%	30
Ranch Hand	14.4%	118	29.4%	979

O = Original Comparison
S = Shifted Comparison
R = Replacement Comparison
A = Air Force Interviewed Comparison

Work absenteeism was assessed by a consideration of reported time loss from work during the 6 months prior to interview. No statistically significant differences were noted between the O, S, R and A group on this parameter (relevant data provided in Table V-12).

Table V-12

WORK LOSS
(NON-BLACK PARTICIPANTS ONLY)

Group	Participants Who Took Questionnaire Only (PC)		Participants Who Took Questionnaire and Physical Examination (FC)	
	Percent with Work Loss	N	Percent with Work Loss	N
O	16.8%	173	20.5%	707
S	14.7%	34	21.1%	152
R	12.0%	75	18.6%	237
A	-	0	23.3%	30
Ranch Hand	18.8%	112	20.3%	955

O = Original Comparison
S = Shifted Comparison
R = Replacement Comparison
A = Air Force Interviewed Comparison

Thus, for the 3 basic variables emphasized for test by the study protocol, the replacement comparisons (S+R+A) were found to be statistically significantly dissimilar from the originals on 1 variable, self-assessment of health. To more fully assess replacement-original differences, 9 additional variables from the questionnaire were examined: (1) household income, (2) participant education (high school or less, greater than high school), (3) participant anger scale, (4) participant psychoneurological erosion scale, (5) participant anxiety scale, (6) participant depression, (7) reported liver ailments, (8) spouse miscarriage rate, and (9) occurrence of acne. The fully compliant non-Black replacements (S+R+A) were observed to be statistically significantly different from the fully compliant original comparison participants as regards education (P = 0.04), anxiety level (P = 0.02), and psychoneurological erosion (P = 0.02). With respect to education 48.8% of the fully compliant replacement comparisons report more than a high school education, while 43.7% of the original comparisons report more than a high school education. Original fully compliant comparisons reported more moderate to severe anxiety than did the replacements (56.9% versus 55.6% respectively). Reported psychoneurological erosion addresses difficulties with mental tasks such as arithmetic work. The replacement comparisons reported erosion more commonly (37.2%) than did the original comparisons (30.2%). These measures of psychological status were not validated as truly measuring their intended end points and they are not necessarily statistically independent of one another, nonetheless, a picture of differences between the comparisons subsets is evident.

Thus, of 12 variables drawn from the questionnaire, 4 variables (reported health status, education, anxiety level and psychoneurological erosion) distinguish the replacement comparisons(S+R+A) from the original comparisons testing at the 0.05 level. The differences observed are not only statistically significant but may also reflect clinically meaningful differences if the self-reporting is accurate. Analyses of bias have also been conducted using physical examination data end points to obtain a firmer evaluation, and these analyses are described in the following paragraphs.

Five laboratory variables have also been examined for evidence of differences among the comparison groups: white blood cell count (WBC), hemoglobin concentration (HGB), total bilirubin (TBIL), serum glutamic oxalic transaminase (SGOT) and lactic dehydrogenase (LDH). This testing is summarized in Table V-13. The analyses were performed with a general linear models program, operating on WBC and HGB in natural units and TBIL, SGOT and LDH in logarithmic units. It is clear from Table V-13 that there is definite indication of comparison group differences.

Table V-13

SUMMARY OF BIAS ASSESSMENTS OF REPLACEMENT COMPARISONS USING LABORATORY MEASURES (NON-BLACK PARTICIPANTS ONLY)

Clinical Variable	Adjusted Mean For Original (O) Comparisons	Adjusted Mean For All Replacements (S+R+A)	P Value For Mean Differential
WBC	7.24	7.78	0.027
HGB	16.0	15.9	0.522
TBIL	0.577	0.609	0.063
SGOT	33.1	32.7	0.498
LDH	142.0	141.2	0.265

Lastly, 13 clinical variables from the physical examination itself were evaluated for O, S, R, A comparison group differences. As summarized in Table V-14, statistically significant differences were found.

Table V-14

SUMMARY OF BIAS ASSESSMENTS OF REPLACEMENT COMPARISONS USING MEASURES FROM THE PHYSICAL EXAMINATION

*1.	Systolic Blood Pressure	No differences detected
*2.	Diastolic Blood Pressure	No differences detected
*3.	Posterior Tibial Pulse	{S statistically different from R + A {O statistically different from R + A
*4.	Dorsalis Pedis Pulse	No differences detected
*5.	EKG	{S statistically different from R + A {O statistically different from R + A
6.	Vibration Sense	{S statistically different from R + A {O not different from R + S + A
7.	Tremor	{S statistically different from R + A {O statistically different from S
8.	Nerve conduction velocity above the elbow	No differences detected
9.	Nerve conduction velocity below the elbow	No differences detected
10.	Peroneal nerve conduction velocity	No differences detected
11.	Full Scale Intelligence Quotient	No differences detected
12.	MMPI Scale D	{S statistically different from R + A {O statistically different from R + A
13.	MMPI Scale L	No differences detected

*Black participants removed.

Taken together the analyses described above imply very strongly that the S, R and A comparison groups are not random samples drawn from the same population as the original comparisons (O). Since the comparison group differences are not observed in all variables studied, a possible approach is to perform a prior test of significance (PTS) to test for appropriateness of replacement use, followed when possible by a Ranch Hand-all comparison test. This use of a PTS has been discussed with appreciable detail in the statistical literature (Bozivich et al, 1956; Bancroft, 1964; Kale and Bancroft, 1967; Arnold, 1970; Cohen, 1974). Recommendations in this literature suggest a preliminary test for combination using an alpha level of 0.25, followed by a test of differences at an alpha level of 0.05. Calculations of study power with and without the PTS have indicated that, given the sample sizes in this study, the PTS only provides partial protection against inferential bias. This result can be understood by reference to Figure V-5 where 2 power curves are given.

Figure V-5

POWER CURVES FOR ALTERNATIVE ANALYTICAL METHODS

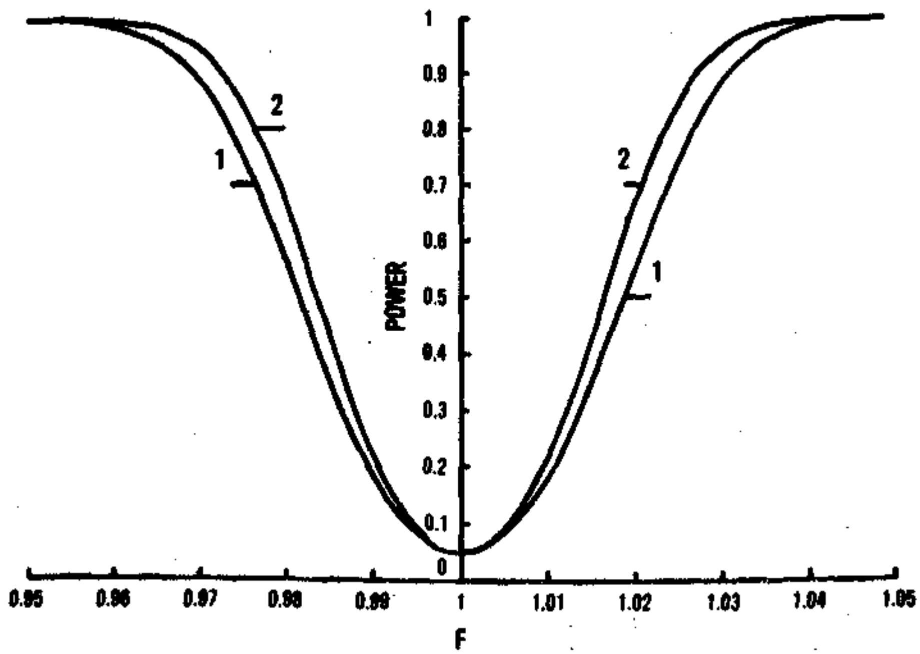


Figure V-5. Curve 1: Power curve for Ranch Hand-original comparison tests on means. Curve 2: Power curve for Ranch Hand-comparison tests on means assuming replacement comparisons are unbiased. F is the symbol for ratios of Ranch Hand-comparison means.

The lower power curve (curve #1) is for a test of difference between the Ranch Hand group (N=1045) and the original comparisons (N=773). The upper curve (curve #2) is for the same test of difference but between the Ranch Hand group and all comparisons (N=1224) assuming that the replacements are unbiased. These curves are drawn for a hypothetical clinical variable with ratio of standard deviation to mean being 0.200. The variable F is the ratio of the exposed mean to the comparison mean. The slight displacement of the 2 curves in the vertical direction (power) is easily negated by small degrees of bias in the replacement comparisons.

The Study Protocol reflects a strong concern for a variety of biases that may be operating in this study. The effect of the potential bias, by using the shifted and replacement members of the comparison group, was not uniformly viewed by the Principal Investigators. Because of time constraints, the Science Panel was not convened to address this complex issue. Instead, a management decision was made to base the primary clinical analyses upon a contrast of the Ranch Hand group and members of the original comparison group. For completeness of data descriptions, some chapters additionally contain analyses founded upon the entire comparison group.

9. Noncompliance Bias

The data in the previous section suggest that a degree of self-selection did occur in association with compliance to the physical examination, indicating that the group who came to physical examination may be biased from the original sample. Since this report emphasizes analysis of data from fully compliant participants, selection biases associated with physical examination compliance are of importance. Table V-15 displays differences between fully and partially compliant study participants.

Table V-15

DIFFERENCES BETWEEN FULLY COMPLIANT
(TOOK QUESTIONNAIRE AND PHYSICAL EXAMINATION)
AND PARTIALLY COMPLIANT (TOOK QUESTIONNAIRE) STUDY PARTICIPANTS:
P VALUES FOR TEST OF NO DIFFERENCE

	Ranch Hand Fully Compliant Versus Partially Compliant	Original Comparison Fully Compliant Versus Partially Compliant
Health Status	0.006	0.004
Medication Use	<0.001	0.23
Work Loss	0.79	0.30
Household Income	0.32	0.86
Education	0.66	0.39
Anger	<0.001	0.01
Anxiety	0.020	0.61
Erosion	<0.001	0.002
Depression	0.007	0.36
Liver Ailments	0.76	0.64
Miscarriages	0.97	0.077
Acne	0.37	0.75

Eighty-seven percent of the Ranch Hand group were compliant to the physical examination while 76% of the original eligible comparisons attended. Let RR_{obs} be the observed relative risk calculated from the physical examination data and RR be the actual relative risk of the originally drawn groups. Direct algebraic considerations provide the relationship

$$RR = \frac{0.13\,\gamma_e + 0.87}{0.24\,\gamma_c + 0.76}\,RR_{obs} \qquad \text{Equation \#1}$$

In this equation, γ_e is the ratio of the prevalence of the finding in the Ranch Hand group noncompliant to physical examination, to the prevalence in Ranch Hand individuals who were examined; the term γ_c is the same ratio for the comparison group. In other words, the values γ_e and γ_c are within-group noncompliant-to-compliant relative risks. The values of γ_e and γ_c are in fact not known so that RR can in fact not be known with exactness. Were $RR_{obs} = 1.00$ and were the finding rate 0.100 in the fully compliant comparison group, γ_e and γ_c could both range from zero to 10, indicating that RR could take values from 0.28 to 2.86. Thus, noncompliance to the physical examination is a serious concern in the attempt to properly infer herbicide effects from group differences noted at physical examination.

It is possible to develop an indication of the magnitude of the within-group relative risks γ_e and γ_c using data from the questionnaire. From Table V-15, it is clear that in several instances (roughly 50%) the fully compliant replacements are not statistically different from the partially compliant or, approximately, $\gamma_e = \gamma_c = 1.0$. In these cases, an observed relative risk, RR_{obs}, is at least approximately equal to the actual relative risk, RR of the original sample. On the other hand, using the health status data, γ_e is estimated to be 0.54 while γ_c is 1.04 for the categories "fair-poor" health, indicating (using Equation #1) that $RR = 0.93\ RR_{obs}$. This result implies the possibility that the use of physical examination data can overestimate a relative risk by 7%. On the other hand, for the erosion scale γ_e is 0.52, while γ_c is 0.63, providing $RR = 1.03\ RR_{obs}$, which implies the possibility that the physical examination could underestimate relative risk by 3%.

These calculations of γ_e and γ_c use questionnaire data, and thus, the results are indications only of bias in the physical examination, due to the extrapolation from 1 data set to another. Nevertheless, the results do indicate a range of bias which is much smaller than the range obtained when no assumptions about γ_e and γ_c are made.

It is difficult to conceive of a partially compliant rate or proportion as being different from a fully compliant rate or proportion by more than a factor of 2. Thus it may be assumed that

$$0.5 \leq \gamma_e \leq 2.0$$

$$0.5 \leq \gamma_c \leq 2.0$$

under this assumption

$$0.75\ RR_{obs} \leq RR \leq 1.28\ RR_{obs}$$

An inequality such as the one above should be applied to each study result reported here to reflect the possible effect of selection bias. If the above inequality is used, the smallest observed relative risk that can be considered actually larger than 1 is 1.33 ($=0.75^{-1}$) and the largest observed relative risk that can be considered actually smaller than 1 is 0.78 ($=1.28^{-1}$). Or, as a simpler rule of thumb, full sample relative risks may be assumed to be within ±30% of observed relative risks. Of course, this measure of uncertainty due to noncompliance must be added to the uncertainty due to finite sample sizes, and to other sources of possible inferential error.

It is not feasible to numerically evaluate the degree of bias in physical examination measurements of continuously distributed variables such as blood pressure, hemoglobin concentration or pulmonary volumes, using questionnaire data, as no analogous values were obtained from the questionnaire. An equation similar to Equation #1 holds for the ratio of group mean values for a continuous variable, namely:

$$RAT = \frac{0.13\ \gamma_e^1 + 0.87}{0.24\ \gamma_c^1 + 0.76}\ RAT_{obs} \qquad \text{Equation \#2}$$

In this equation, RAT_{obs} is the ratio of the Ranch Hand fully compliant mean to the comparison fully compliant mean, RAT is the ratio of the means of the complete original samples, γ_e^1 is the ratio of the partially compliant mean to the fully compliant mean in the Ranch Hand set and γ_c^1 is the same ratio for the comparison participants. Estimates of γ_e^1 and γ_c^1 are not available; however, it is difficult to conceive of a partially compliant mean as different from a fully compliant mean in the same group by more than 20%; whence, we assume:

$$0.80 \leq \gamma_e^1 \leq 1.20$$
$$0.80 \leq \gamma_c^1 \leq 1.20$$

Under this assumption

$$0.93\ RAT_{obs} \leq RAT \leq 1.08\ RAT_{obs}$$

that is, full sample ratios are anticipated to be within ±8% of observed sample ratios of means. The potential error in sample mean ratios portrayed above must be considered by the reader in the interpretation of mean shift data presented in this report.

10. Summary and Conclusion

The comparison group in this study is divisible into 3 subgroups: original comparisons, shifted comparisons and replacements. Due to study implementation and contractual constraints, the shifted and replaced comparison groups were scheduled differently from the original comparison group for the study questionnaire and physical examination. The original comparisons were handled in a manner essentially identical to that of the Ranch Handers.

Analysis has shown that replacements differ from original comparisons on compliance to questionnaire and physical examination; however, shifted comparisons are not statistically significantly different from originals on these parameters. Both shifted and replacement comparisons have been found to be statistically significantly different from the original comparisons on a variety of questionnaire and physical examination measures. This source of potential bias is completely avoided in this report through the primary use of the original comparisons in hypothesis testing.

Differential compliance to the physical examination occurred with 87% of the Ranch Handers and 76% of the comparisons attending. This fact raises the concern for a second bias which cannot be avoided, and it could be a result of media and Ranch Hand Association support for this study. It is suggested, however, that this bias is not large. Worst-case estimates imply that observed relative risks are displaced from correct relative risks by no more than 30% by noncompliance effects, and observed mean ratios are displaced by no more than 8%.

Chapter VI

QUALITY CONTROL PROCEDURES

Quality control aspects of the Air Force Health Study have been of major importance since the inception of the study design. The focus of quality control concerns has been 1) to ensure the highest quality and validity of this study, 2) to reduce variability and bias in all data, 3) to validate all statistical methods and enhance statistical power wherever possible, and 4) to protect government resources. The purpose of this chapter is to present a categorical overview of the quality control procedures and to present representative data, where appropriate.

1. Prestudy Considerations

The Study Protocol was formulated and refined in 1979-1980, during which time it underwent 4 independent peer reviews and a final review and approval by the Science Panel of the Agent Orange Working Group. Knowledge gained from visits to national and international herbicide dioxin experts was also instrumental in refining the Protocol.

Initial contract management aspects were handled on a scientific business basis. The Principal Investigators developed comprehensive statements of work with specific evaluation criteria. All contract proposals were evaluated without reviewer knowledge of the proposer and then scored independently on their scientific and business merits. Contracts were awarded on the basis of scientific and medical quality; price considerations were secondary. Fixed-price competitive contracts were written where feasible. During the conduct of the contracts, numerous scientific and business meetings were held with the contractors in an attempt to ensure quality and timeliness of the data. Scientific concerns continued as the primary emphasis throughout the periods of contract performance.

The population ascertainment process for both the Ranch Hand and comparison groups has continued for over 4 years. Extensive computer searches and a hand review of all available military personnel records have assured an almost complete and comparable identification mechanism. In addition, individual responses to the Ranch Hand Reunion Association and wide media coverage of the Agent Orange issue have greatly assisted both the ascertainment and address-update processes. A few potential study participants whose records were burned in the National Personnel Record Center remain uncategorized at this time. Both populations were subjected to a rigorous systematic location process (see Chapter III), resulting in a location efficiency of 99.5%; this achievement has eliminated population selection bias and has afforded each individual a maximum opportunity to participate in the study. The computer technique to match each Ranch Hander to a comparison individual by job category, race, and age to the closest birth month was exceptionally rewarding, as about 70% of the matches were exact to birth month and year, as well as to job and race. Such precision has enhanced the analytic flexibility of the statistical techniques cited in this report.

2. Questionnaire Data

The quality of questionnaire data was enhanced by 2 distinct mechanisms: 1) all questionnaire instruments were designed by nationally recognized survey research organization; and 2) the instruments were administered in an in-home setting by another outstanding survey research firm. A minimum number of highly qualified interviewers were used to reduce data variability, and the interviewers were blind to the exposure status of the respondent. In addition, the interviewers were specially trained and then race matched to the study participants, where possible. Spouse fertility data was obtained independently of the male interview but within the same interview setting.

The data collection verification process was conducted sequentially. The Louis Harris Associates Incorported (LHA) field interviewer completed a questionnaire thoroughness edit, followed by a Central Office thoroughness check and appropriate editing. Participants were recontacted by phone, when necessary. LHA trained the United States Air Force interviewers and project staff to complete the identical sequential process. A double blind key punch system was used for both the LHA and USAF collected questionnaire data. Range checks identified outliers, and discrepancies were resolved. The contractor randomly validated completed interviews by phone; however, these interviews have not been analyzed for this report. An early USAF sampling review of the data revealed key punch error rates in specific sections of the questionnaire that ranged from 0 - 1.4%. The USAF systematic review and recoding of all medical areas included in this report have reduced these error rates. Further, subsequent to the questionnaire, each participant's military personnel record was hand reviewed, in order to provide exact data in the time and location of military assignments. These data have been used in this report in lieu of the memory-dependent military duty information obtained by the questionnaire.

Most study-participant questionnaire data were designed to be cross-referenced to review-of-systems data and physical examination findings. A notable exception, fertility birth defect data, will be validated by birth certificate or medical records, if retrievable. Female response data were used in all fertility/birth defect analyses, when available. In instances of multiple marriages and offspring, unexpected difficulty was often encountered in assigning a child to the correct spouse pair. Such discordant results were resolved by a hand review and computer input of the questionnaire data. Thereafter, this system supported all offspring data for analyses herein. Next-of-kin interview data will be verified by cross reference to the deceased's medical records. No attempt was made to validate the abbreviated noncompliant questionnaire because of the individuals expressed disinterest in the study.

3. Physical Examination Data

The bulk of scientific data of most concern to the public and veterans will stem from the physical examinations in this study. Consequently, great emphasis has been placed upon quality control of the physical examination and laboratory procedures.

All examinations were conducted at a single site by a contract medical organization of unquestioned reputation. The contractor was required to provide board certified physicians for the examination. Dermatologists were required to attend a 1-day intensive training session on the diagnosis of chloracne. A minimum number of physicians and paramedical staff was used to reduce data variability. The credentials of each physician and senior psychologist were submitted to the Air Force for approval. The contractor fulfilled the commitment to maintain a stable work force throughout the contract, best exemplified by the facts that (1) approximately 90% of the general physical examinations were conducted by one internist, (2) all electromyographic tests were performed by one technician using a single constantly calibrated machine, and (3) 90% of the final diagnostic assessments were made by 2 internists (master diagnosticians). All medical examiners were required to adhere strictly to the physical examination specifications as cited in the Study Protocol and were not permitted to evaluate a participant outside of his medical specialty area. Thus, each examiner was blind to examination findings outside his area of expertise, as well as to the exposure status of each participant. An Air Force physician, serving as an on-site physician monitor, conducted frequent inspections of all aspects of the physical, psychological, and laboratory examinations to ensure contract compliance and to approve further diagnostic workups for those participants exhibiting serious medical findings. Further, the Air Force monitor was periodically supplemented by Air Force consultant physicians in the areas of internal medicine, cardiology, dermatology, psychiatry, psychology, immunology, and laboratory medicine. For study participants crossing 2 or more time zones, 1 to 4 additional rest days were provided before the examination, in order to standardize psychological and laboratory parameters. All examination data were provided to the diagnostician who confirmed significant positive findings and formulated a diagnosis, if one was warranted. The diagnostician then carefully debriefed the participant and recommended follow-up medical action, if indicated. Electrocardiograms (ECG's) on all participants were sent to the Clinical Sciences Division, USAF School of Aerospace Medicine for cross-reference to the USAF ECG Repository. All data from the examination was collated and checked for completeness; this process was rechecked prior to submission to the data processors. Computer entry of all data was made by a single key-to-disk entry with hard copy verification; visual range checks were accomplished prior to transmittal. The Air Force data processors conducted a small sampling from the data set and detected sectional error rates ranging from 0.2 - 1.3%, with 6 of the 7 sectional rates ranging from 0.2 - 0.4%. Plausible ranges were established for most variables and all data outside this range were verified against the hard copy of the examination. All discordant transcription errors were corrected; otherwise, the data were accepted as correct. Inconsistent dates were corrected, where possible. All data sets or subsets were checked for reasonability and, in many cases, the information was verified by the hard copy of the examination.

4. Laboratory Procedures

Because the thrust of the physical examination was to cast as wide a clinical net as possible, the importance and number of laboratory tests were substantially increased over an ordinary diagnostic or screening examination. Thus, all contract and subcontract laboratories were required to be licensed and certified by the College of American Pathologists or by the Centers for Disease Control under the Clinical Laboratory Improvement Act of 1977. For the laboratory battery of 36 tests, each responsible contract or subcontract laboratory was required to maintain quality control data for audit. The bulk of nonradioassay procedures was accomplished at the contract clinic; a DuPont Automated Chemical Analyzer III (ACA) and Hemalogs 890 and D90 Automated Counters performed the majority of tests. For the ACA, reagents of the same lot number were used throughout the study period. Stringent research grade coefficients of variation (CV's) were required for most assays (see Appendix XV), often necessitating repeat runs to meet these standards. Where available for specific assays, trilevel controls were run at intervals of every 10th specimen, and 1 specimen set of every 15th was run in duplicate. These results were used to generate cumulative sum quality control charts to determine if test systems drifted significantly out of control over time since the CV's are relatively insensitive to trends over time. Of the 14 assays with CV requirement standards, 7 were significantly ($P < .05$) out of standard at 1 or more levels. On-site visits and detailed power calculations with respect to detecting differences between means showed that these variances would not substantially or biologically alter group comparisons or conclusions. Adjustment of study participant clinical values for drift and other variations in laboratory control levels was considered, but was determined unnecessary. This decision was made by evaluating participant and laboratory quality control values for High-Density Lipoprotein (HDL). Deviations were computed from each overall tri-level mean and these were substracted from each participant's value. The distributions with and without adjustment were then contrasted. The results are tabulated below:

Table VI-1

HDL VALUES ON 2227 PARTICIPANTS (mg/100 ml)

	Original Value	Adjusted Value
Mean	46.18	46.12
Standard Deviation	12.61	12.72

No increase in HDL precision is noted. In fact, a small increase in the standard deviation was found, clearly indicating that adjustment would not improve the ability to detect group differences.

Immunologic assessments were performed by subcontract on 592 participants. Participants were randomly selected (terminal digit of their random study number) midway through the physical examination contract. The subcontractor was blind as to the exposure status and group membership of each individual. The functional capacity of lymphocytes to respond to mitogens or antigens and the number of T and B lymphocytes were measured in isolated peripheral blood. An Immunologic Peer Review Group (see Appendix I) was convened on-site to review technical procedures and to develop analytic strategies. This panel determined that 56 of the 592 samples were not processed due to technical errors in specimen handling. The procedure used for isolation of purified mononuclear cells was substandard. This resulted in cell populations which were depleted of adherent mononuclear cells and contaminated with polymorphonuclear leukocytes and red cells. Differential counts on purified cells were not accomplished so that the actual number of nomonuclear cells used for each assay was not determined. A number of the lymphocyte function assays had excessive variation, manifested by a coefficient of variation (CV) greater than 15%, as reflected in Table VI-2.

Table VI-2

PERCENT OF GROUPED LYMPHOCYTE FUNCTION ASSAYS EXCEEDING A CV OF 15%

Functional Test	Percent
Concanavallin A	15.8
Phytohemagglutinin	20.3
Tetanus Toxoid	75.7
Pokeweed Antigen	10.2

Although CV's were excessive, these variations appeared to be randomly distributed since there were no observed trends over time and there were no differences in error distribution between groups. Only 11 duplicate specimens were received (1 per 50 specimens). Intraspecimen reproducibility was impaired and several split samples varied by more than 50%. Similarly, intraspecimen reproducibility was reduced and represented sporadically within the data set. Further, 54/432 specimens (12.5% of the total) had a ratio of concanavallin A to phytohemagglutinin less than 0.30, indicating mitogen dysfunction rather than failure of lymphocytes to respond to mitogen. The low levels of stimulation observed in many tetanus toxoid-stimulated cultures additionally suggested that caution should be used in the interpretation of the functional results. Accordingly, the Immunology Peer Review Group recommended that the lymphocyte function data not be used clinically to determine the immune status of an individual participant. Further, the panel recommended that the functional data set be used only to evaluate differences, if any, between the Ranch Hand and comparison groups.

The T and B lymphocyte enumeration studies demonstrated acceptable reproducibility and acceptable daily and long-term variations between the total T lymphocyte (T_3) and the sum of lymphocyte subsets (T_4 and T_8). Criteria for exclusion of T and B lymphocyte data were (1) samples exhibiting greater than a 30% background fluorescence (11 samples or 2%), and (2) samples with a T_3 or T_{11} proportion of less than 10% (7 samples or 1.3%). Although differential counts were not performed initially on the Ficoll-hypoque separated cells, sufficient paraformaldehyde-stored cells were available after conclusion of the contract to permit a 250 cell differential count on 525 of the 592 specimens.

This count permitted the calculation of absolute T and B lymphocyte numbers. After application of acceptibility criteria, cell count data were available on 490 specimens.

5. In-House Data Collection and Statistical Analysis

The complexity and time constraints of this study have made it impractical to hire a series of contractors and expect them to accomplish integrated and timely work. Thus, the Air Force investigators and technical staff have assumed major roles in the areas of population ascertainment and location, verification of eligibility in the study, medical record and personnel record validations, determination of replacements, examination scheduling, medical coding, repository formation, and statistical analyses. Where at all possible, in-house actions have been documented by coding schemes, decision rules, user manuals, and computer audit trails. It is our desire to submit duplicate unedited copies of all contractor data tapes to the Advisory Committee for storage and any possible later use.

The data repository task has been monumental. All medical coding has been accomplished in duplicate with resolution of disputes. All in-house gathered data have been subjected to 100% echo and consistency checking. Subsamples have been obtained to develop quality control error rates. Backup hard copies have been created for all data bases in the event of computer loss or malfunction.

The statistical approach to this study consists of a preset state-of-the-art framework. The statistical strategy was detailed before the data were reviewed or the group membership codes broken. Both external peer review and internal reviews (conducted by civilian consultants) have validated our approaches. Computer software have been extensively validated by using mock data sets.

Chapter VII

STATISTICAL METHODS

1. Statistical Study Design

Study data fall naturally into 3 classes: data addressing symptoms, as reported by the subject at questionnaire or in the medical history; data addressing medical signs, determined at physical examination or by review of medical records; and data addressing mortality. A fully expressed or overt herbicide effect would be characterized by increased mortality and more signs and symptoms in the Ranch Hand group as contrasted with the comparison group. These effects should increase with increasing exposure to herbicide. As defined in the study protocol, a subclinical herbicide effect should not be associated with increases in mortality or symptom reporting, but should be found as increases in abnormal findings on physical examination of exposed personnel. These abnormal findings should be more common in the subset of individuals most highly exposed.

Symptom reporting is subjective by definition and, thus, subject to influences that could significantly impair proper inference. For example, a stoic and/or highly patriotic individual might unconsciously or consciously suppress the expression of symptoms. Similarly, anxiety associated with middle or older age could prompt elaboration of symptoms. Association of increased symptom reporting with increasing herbicide exposure is suggestive of a true herbicide effect but is not strongly confirmatory as exposed personnel are at least partially aware of the degree of their exposure and could be suppressing or elaborating symptoms in terms of their perceived exposure.

The study design permits a specific check on the possibilities of overreporting or underreporting of symptoms. The technique involves contrasting the incidence of physical findings when symptoms are present, between the Ranch Hand and comparison groups. The policy followed in this report is that, if there are no group differences in the sign to symptom ratio, underreporting or overreporting is considered unlikely. If there are group differences in the sign to symptom relationship, underreporting or overreporting is possible, but medically, a real group difference may still exist. Overreporting can be assessed by contrasting reported illness with the results of the physical examination and by medical record reviews. However, this assessment is much more difficult for reported psychological symptoms, since a record of hospitalization, the most reliable indicator of verified illness, occurs only in the most severe forms of psychological illness.

2. The Need for Adjustment Procedures

When samples are drawn from a very large or potentially infinite population of individuals, 2 samples of equal size rarely display the same number of diseased individuals. Thus, when comparing 2 groups of individuals, one must ascertain whether the differences are or are not compatible with differences due to random sampling. Two groups of individuals are said to be statistically significantly different when the differences between the groups cannot be accounted for by random sampling or chance mechanisms. If 2 groups are statistically significantly different and 1 of the groups has experienced a specific exposure, this is suggestive that the exposure and the disease may be causally related. However, great care must be exerted in this setting since other unevaluated factors may be the true cause of the observed group differences, and group difference is only 1 element in the causal chain.

Adjustment procedures are those statistical procedures which allow objective treatment of intervening variables which can distort the true herbicide effect, if one is, in fact, present. Failure to deal with an important intervening variable can either, induce a false effect or obscure a bona fide effect. Statistical procedures for ascertaining statistical significance and for adjustment used in this report are briefly outlined in a subsequent section of this chapter.

The presence of intervening variables occurs either because the sampling procedure used was not completely random or because, by chance, widely different cohorts have been drawn. Matching is a statistical procedure which can partially protect against intervening variables. In this study, the exposed and comparison cohorts were matched on age, race and military occupational category.

Intervening variables are also called covariables, risk factors, or substitution variables, depending on the literature consulted. There currently exists no objective method for ascertaining that all relevant intervening variables have been accounted for. When all known intervening variables have been examined, there is some degree of comfort that observed relationships are correct. Small sample sizes can, however, markedly inhibit study of intervening variables.

A type of intervening variable that is of special interest is the confounding variable (Kleinbaum et al, 1981; Anderson et al, 1980). A confounding variable is an intervening variable that is associated both with the disease under consideration and the exposure categories being used in the study. Failure to adjust for the confounding variable means that the estimated exposure-disease association may be biased. Nonconfounding intervening variables, on the other hand, affect the precision of estimated exposure-disease associations.

In the context of intervening variables or covariables, the concept of interactions is important (Kleinbaum et al, 1982). Interaction occurs when the statistical distribution of a random variable (such as a relative risk, or the difference between group sample means) is a function of a second variable (such as age or weight). The study of interactions in a data set is important for it may lead to the discovery of subpopulations at increased or decreased risk from the population taken as a whole. Confounding and interaction can occur together or separately.

The use of 1 or more measures of exposure (exposure indices) is an extremely useful addition to the study of group differences. Supplementing the analysis of group differences, the use of exposure indices looks within the exposed group to determine whether the more highly exposed individuals tend to exhibit more disease or abnormalities. The use of exposure indices provides a potentially tighter assessment of herbicide exposure. However, by working with the Ranch Hand group, primarily, sample size limitations also impact this technique. Also, use of exposure indices does not obviate the need to be concerned with confounding and other intervening variables. The construction of exposure indices for the Ranch Hand II study is described in another section of this report.

3. Overview of Specific Statistical Methods

In this report, log-linear models have been used when the dependent variable under consideration was categorical or made categorical. Covariables that are intrinsically continuous were stratified for use as adjusting variables in the analysis. Most of the analyses presented in this report are unpaired analyses and, thus, do not fully exploit the paired design of the study. Prior to performing a paired analysis that collapses over matching variables, it is important to determine that the matching variables do not interact with the exposure variable in affecting the dependent variable. The tests presented in this report include these assessments of interaction and, thus, are the early stage of a full paired analysis, as well as being useful for inference in their own right. When unpaired analyses are performed on paired data, there is a consequent loss of test power and less of a chance of detecting a herbicide effect, if one exists. However, an unpaired analysis can actually be more powerful than a paired analysis if study noncompliance or other causes of missing data have resulted in large numbers of broken pairs (Bishop, et al, 1975). The software package used to perform the log-linear analyses in this report is BMD-P4F. In all analyses, the hierarchical modeling procedure was used which starts by examining all covariates and collapses across covariates only when relevant interactions are noted to be null.

Whenever the dependent variable was a continuous variable and the covariables were a mixture of categorical and continuously distributed values, regression, multiple regression and/or general linear models were used (e.g., GLM of the Statistical Analysis System). In these analyses in the report, the covariables were always entered as linear terms only. Also, unless otherwise noted, all group-by-covariate terms (interaction terms) were used in all models.

When group comparisons were made without adjusting for intervening variables, simple parametric tests were used, such as the statistic assuming underlying normal distributions. When it was judged that parametric assumptions were not reasonable, the hypothesis of no difference between Ranch Hand and comparison distributions was tested by the Kolmogorov-Smirnov Two-Sample Test (Gibbons, 1971).

In this study, a very large amount of data has been collected on each participant. In this report more than 190 dependent variables were tested. Testing at the 0.05 level means that in 5 out of 100 instances where there has actually been no association, an association will be falsely inferred. The picture is more complex in this report, since as with many epidemiologic studies, measures are not independent but are highly associated. Those variables thought to be most associated with one another have been grouped into clinical categories and these are used for reporting; e.g., general health, psychology, neurology, etc. However, it cannot be assumed that the clinical categories are completely independent from one another. Within each clinical category, whenever possible, summary indices have been developed to provide an overall view of participant status and lessen the likelihood of false inference. Another important concept which protects against false attribution of herbicide effect is careful consideration of the pattern of statistically significant results. If a herbicide effect is being falsely inferred, it might be in a direction opposite to that expected from prior reports. On the other hand, if a test is found significant with a high degree of confidence, its credibility must be considerably enhanced.

The inverse of falsely attributing a herbicide effect is the problem of failing to detect an effect when one actually exists. This involves the questions of study power. Power is addressed at length in the study protocol but an overview is provided in this chapter. Under the condition of equal Ranch Hand and comparison group sizes, and assuming unpaired analyses, Table VII-1 provides the approximate sample sizes needed to detect specific relative risks with approximate probability 0.80 ($\alpha = 0.05$). The present study is able to detect (with probability 0.80) those relative risks enclosed below the heavy line drawn through the table. Study power for continuous variables is shown in Table VII-2. The mean shift refers to the displacement of the Ranch Hand mean relative to the control. The variables considered are normally distributed, and unpaired testing is assumed in the table. The present study has approximately an 80% chance of detecting mean shifts below the heavy line drawn through the table.

One thousand forty-five Ranch Handers complied to the physical examination in this study. With this size group, disease states with a cumulative incidence in the group of 1/500 or less have a 10% chance or greater of no cases at all being encountered. More detail on this point is given in Table VII-3 where the probability or seeing no cases at all is provided for other cumulative incidence values.

Another view of study power can be obtained through use of the P values reported in this volume. These observed probabilities permit a direct evaluation of study power against the alternative hypothesis defined by the observed statistic. For example, in categorical tables, the chi-square statistic can be inferred from the cited P value. This observed chi-square statistic can be used as the alternative hypothesis to the null hypothesis of statistical independence. Taking the observed chi-squared statistic as the noncentrality parameter in the appropriate chi-squared distribution, a calculation of study power against the observed effect is possible (Johnson and Kotz, 1970). Table

VII-4 provides a short summary of P-value power relationships. Using Table VII-4, if a P-value of 0.10 is reported from a 2X3 table categorical analysis, it may be inferred that study power against the observed effect was 47% (using the two degrees of freedom column in the table). This implies that, if the groups are really as different as they appear from the data, this difference would be detected as statistically significant 47 times out of 100 hypothetical repetitions of this study.

Table VII-4 can also be used to approximately assess the power of linear model analyses. The test statistic in these analyses is an F distribution associated with γ_1 and γ_2 degrees of freedom. The degrees of freedom, γ_2 associated with dependent variable mean squared error is usually quite large in this study. Thus the $F(\gamma_1,\gamma_2)$ distribution can be usually well approximated by a $\chi^2(\gamma_1)$ distribution. The degree of freedom, γ_1, will be 1 when equality between 2 variables such as slopes or group means is under test, and will be the number 2 when equality between 3 variables is under test, as in the trilevel exposure index case.

Table VII-1

NEEDED SAMPLE SIZES TO DETECT EXPOSURE EFFECTS
IN TWO SAMPLE TESTING ASSUMING EQUAL SAMPLE SIZES*

DATE OF DISEASE IN CONTROL POP = P CONTROL	MULTIPLIES FACTOR IN EXPOSED GROUP = RELATIVE RISK										
	1.25	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00
$\frac{1}{10000}$	1,408,647	388,536	114,381	36,618	19,623	12,843	9,339	7,244	5,869	4,905	4,196
$\frac{1}{5000}$	704,244	194,244	57,182	18,306	9,809	6,420	4,668	3,621	2,933	2,451	2,097
$\frac{1}{1000}$	140,722	38,810	11,423	3,656	1,958	1,281	931	722	585	489	418
$\frac{1}{500}$	70,282	19,381	5,703	1,824	977	639	464	360	291	243	208
$\frac{1}{100}$	13,930	3,838	1,127	359	192	125	90	70	56	47	40
$\frac{1}{50}$	6,886	1,895	555	176	94	61	44	34	27	22	19

*This study has unequal sample sizes; therefore these tabled values are underestimates.

Table VII-2

NEEDED SAMPLE SIZES TO DETECT EXPOSURE EFFECTS
IN TWO SAMPLE TESTING ASSUMING EQUAL SAMPLE SIZES*

MEAN SHIFT	VARIABILITY (σ/μ)				
	.05	.10	.25	.50	.75
0.5%	785	3,140	19,628	78,510	176,647
1.0%	196	785	4,907	19,628	44,162
1.5%	87	349	2,181	8,723	19,628
2.0%	49	196	1,227	4,907	11,040
2.5%	31	126	785	3,140	7,065
5.0%	8	31	196	785	1,776
7.5%	4	14	87	349	785
10.0%	-	8	49	196	442

*This study has unequal sample sizes; therefore these tabled values are underestimates.

Table VII-3

PROBABILITY OF ZERO CASES AS A FUNCTION
OF CUMULATIVE INCIDENCE

Diease Prevalence	Probability of Finding Zero Cases in a Group of 1045 Participants
1/10,000	.901
1/5,000	.811
1/2,000	.593
1/1,000	.351
1/500	.123
1/200	.005

Table VII-4

STUDY POWER AGAINST OBSERVED EFFECTS

OBSERVED PROBABILITY (P- VALUE) ↓	DEGREES OF FREEDOM			
	1	2	3	4
.001	.908	.924	.938	.948
.01	.730	.780	.816	.845
.05	.500	.583	.642	.689
.10	.376	.470	.536	.590
.25	.210	.300	.367	.425

Study power can be severely influenced by the analytical or statistical method brought to bear on the data. For example, in an evaluation of blood pressure, very small differences in group mean blood pressure can be detected using parametric or nonparametric testing of measures of location; however, if group differences in hypertension prevalence are analyzed, a lesser or no group difference might be found using categorical statistical methods such as log-linear models. In general, there is less power to detect a group difference in specific medical diagnoses of a disease state with categorical procedures, than with the underlying continuous variable. However, even in the absence of statistically significant differences in disease rates, group differences in means and variances are still indicative of differences in disease rates that might be detected if sample sizes were larger. Because of these considerations, analyses in this report of continuous variables and the associated normal-abnormal categories are both provided wherever possible.

4. Verification By Medical Records and Interpretive Precision

This report contains a retrospective morbidity element since both the questionnaire and physical examination inquire about illnesses or medical conditions that may have occurred in the participant prior to this study. These reports of illness are currently being verified by medical record. The study plan additionally includes verification of negative responses. In this report, some reported conditions have been verified by medical record but no verification of negative responses is currently available. This correction of false positives improves the hypothesis testing only if the false negative rate can be assumed negligible, perhaps a reasonable assumption in a military population. If the false negative rate is not negligible, significant bias and loss of precision remains in the hypothesis test.

Chapter VIII

EXPOSURE INDEX DEVELOPMENT

A potential link of clinical end points with herbicide exposure can be tested within the Ranch Hand cohort by using a measure of exposure (exposure index). In general one would search for increasing indications of illness at higher levels of exposure. However, exceptions to this assumption of a consistently increasing dose-response curve are possible through a variety of biomedical mechanisms.

The exposure index used in this report relates to the TCDD-containing herbicides: Herbicide Orange, Herbicide Purple, Herbicide Pink and Herbicide Green. Archived samples of Herbicide Purple suggest that the material had a mean TCDD concentration of approximately 33 ppm and that Herbicide Orange had a mean concentration of 2 ppm. Herbicides Pink and Green contained twice the TCDD of Herbicide Purple and therefore have been estimated to contain TCDD at a concentration of approximately 66 ppm.

The index used in this report is written below:

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

The TCDD Weighting Factor is 24.0 or 1.0, depending on whether the material sprayed was sprayed before or after 1 July 1965. The weighting factor of 1 is used for the period after 1 July 1965, as the HERBS TAPE and other documentation (Young et al, 1978) show only Herbicide Orange being disseminated by Air Force-flown, fixed-wing aircraft at that time. Prior to 1 July 1965, procurement records and dissemination information show that a combination of Green, Pink and Purple was procured and sprayed by Air Force individuals in Vietnam. Using available data (Young et al, 1978) on gallons of Green, Pink and Purple procured and sprayed, a mean of 48.0 ppm was established for the time period prior to 1 July 1965. Dividing by 2 to normalize to Herbicide Orange, the weighting factor becomes 24.0 (i.e., 48/2 = 24/1).

The dates of each subject's tour(s) in the Republic of Vietnam were determined by a manual review of military records. The HERBS TAPE was used along with Contemporary Historical Evaluation and Combat Operations (CHECO) Reports and quarterly operations reports to construct a table of gallons of TCDD-containing herbicide sprayed for each month during the operation. These data are shown in Table VIII-1. For Herbicide Orange missions actual gallons are shown; while for Herbicides Purple, Pink and Green the factor of 24.0 is already included making these effective Herbicide Orange or equivalent Herbicide Orange gallons (TCDD at 2 ppm). The CHECO Reports and quarterly operations reports were used in addition to the HERBS TAPE, as the HERBS TAPE currently available does not list all pre-1965 spray missions. Again, only fixed-wing spray missions are compiled in Table VIII-1, as Ranch Hand personnel were not involved with helicopter and other spraying (e.g., backpack). Also provided in Table VIII-1 are Ranch Hand manning in each occupational category by month, as derived from a review of military records. A computer program was written to address this table with each subject's tour dates to the nearest month, to calculate his exposure index in effective or equivalent Herbicide Orange gallons.

The exposure index reflects the effective number of gallons of Herbicide Orange to which the airman was potentially exposed, where exposure to the higher TCDD-containing herbicides (Purple, Pink, Green) has been properly weighted to place them on the same footing as Herbicide Orange.

As seen by examining the above index definition, the index developed should correlate with the individual's exposure but cannot be an exact measure of actual exposure or body burden. The index is an estimate only, since TCDD concentration is known to have varied across herbicide lots, and since the index does not reflect exceptional exposures such as aircraft hits by enemy fire or dumps (these events are essentially assumed equally distributed). Additionally, the index reflects potential exposure only and does not address specific and determining details of the actual contact. While the index certainly contains errors when applied to judge the exposure of a specific individual, in studying groups of individuals epidemiologically, as in this report, these individual errors are expected to balance out or statistically cancel to a great extent, providing some degree of useful inference.

The numeric exposure index calculated by the procedure described above was subsequently categorized into 3 levels (Low, Medium, High) for use in statistical analyses; and, this categorization was accomplished in a different manner for each Ranch Hand occupational category in order to optimize study capability to detect a herbicide effect. Details of the exposure categorization are as follows.

The study design called for 5 occupational categories: (a) officer-pilot, (b) officer-navigator, (c) officer-other, (d) enlisted-flying, and (e) enlisted-ground. For all exposure index analyses presented in this report, only 3 occupational categories are employed. Specifically all officers were combined into 1 class titled "officer". This combination was accomplished since navigators and pilots were exposed in the same manner, and since individuals in the "officer-other" category were administrators whose exposure was considered effectively zero. Additionally, in the enlisted-ground group, all administrative personnel were assigned a zero exposure value. Under these basic rules, the categorizations shown in Table VIII-2 were developed. A very balanced membership in each occupational category has been provided for each exposure level, optimizing statistical ability to detect a herbicide effect if one exists.

Table VIII-1

HERBICIDE ORANGE EQUIVALENT GALLONS AND RANCH HAND MANNING BY MONTH

Mo/Yr	Gallons Sprayed	Pilot (Occ 1)	Navigator (Occ 2)	Other Officer (Occ 3)	Flying Enlisted (Occ 4)	Other Enlisted (Occ 5)
10/61	0	0	0	0	0	0
11/61	0	5	1	1	6	14
12/61	0	9	2	1	7	20
01/62	191426	14	2	1	7	23
02/62	324216	14	2	1	7	23
03/62	191426	15	2	1	7	20
04/62	0	16	2	1	6	14
05/62	0	15	3	1	6	13
06/62	0	12	2	0	5	7
07/62	0	13	2	0	5	4
08/62	0	11	2	0	5	5
09/62	334126	12	2	0	5	6
10/62	334126	9	1	0	5	6
11/62	0	10	0	0	5	5
12/62	90879	8	0	0	4	5
01/63	0	9	0	0	5	4
02/63	0	7	1	0	5	4
03/63	0	12	1	0	5	6
04/63	0	12	1	0	5	6
05/63	0	10	1	0	5	7
06/63	174024	10	1	0	4	7
07/63	259150	11	1	0	8	6
08/63	0	8	0	0	8	4
09/63	0	10	1	1	9	4
10/63	339588	7	1	1	9	6
11/63	377172	6	1	1	10	6
12/63	942630	5	1	1	6	6
01/64	121454	7	1	1	7	5
02/64	363758	5	1	0	7	4
03/64	755312	8	1	0	5	4
04/64	56799	9	1	0	6	2
05/64	152271	10	2	0	5	2
06/64	612709	7	3	0	5	2
07/64	282789	9	3	0	6	3
08/64	777669	9	3	0	5	3
09/64	1413945	8	3	0	4	2
10/64	1413945	9	3	0	4	2
11/64	1413945	11	3	0	4	1
12/64	1413945	10	3	0	6	1
01/65	1296116	11	4	0	6	1
02/65	1437510	12	5	0	6	1
03/65	730538	13	4	1	6	1
04/65	659841	14	3	1	6	2
05/65	1767431	15	4	1	6	2
06/65	0	16	4	1	7	4
07/65	942630	19	4	1	7	3
08/65	26500	19	4	1	7	3
09/65	44650	22	4	1	6	3
10/65	78850	23	4	1	6	6
11/65	106900	24	6	1	10	12
12/65	148525	23	5	1	11	12
01/66	152450	21	6	1	10	16
02/66	129150	22	6	1	10	26
03/66	135600	21	4	2	10	32
04/66	141050	22	5	2	10	37
05/66	183900	21	6	2	9	38
06/66	191830	20	6	2	10	41
07/66	112300	21	8	2	9	45
08/66	192050	26	8	2	11	46
09/66	213970	28	9	2	12	62
10/66	122040	34	8	3	16	85
11/66	164800	41	8	4	18	104

Table VIII-1 (Cont'd)

HERBICIDE ORANGE EQUIVALENT GALLONS AND RANCH HAND MANNING BY MONTH

Mo/Yr	Gallons Sprayed	Pilot (Occ 1)	Navigator (Occ 2)	Other Officer (Occ 3)	Flying Enlisted (Occ 4)	Other Enlisted (Occ 5)
12/66	212100	45	9	5	28	123
01/67	202360	49	9	5	28	123
02/67	363830	59	13	5	28	116
03/67	285400	51	13	4	28	114
04/67	208300	50	14	4	33	108
05/67	251320	53	15	4	34	101
06/67	335860	55	13	3	36	105
07/67	253884	51	15	3	37	163
08/67	162895	63	13	4	32	160
09/67	298615	60	18	5	33	161
10/67	265335	55	19	5	36	149
11/67	372425	55	17	6	33	145
12/67	383605	58	18	6	34	129
01/68	333595	54	19	6	33	127
02/68	27450	65	19	6	35	141
03/68	48200	69	20	5	34	160
04/68	307740	72	20	6	36	161
05/68	336300	75	18	6	32	160
06/68	226325	77	18	6	37	164
07/68	258100	84	19	7	42	187
08/68	289160	91	18	9	45	192
09/68	216300	89	22	8	44	147
10/68	72250	89	20	8	49	155
11/68	189100	101	17	7	53	153
12/68	218750	94	17	8	51	154
01/69	264450	98	19	7	51	154
02/69	197450	91	18	5	51	166
03/69	356500	90	17	5	53	172
04/69	339800	94	20	6	54	161
05/69	353800	93	19	6	54	151
06/69	383533	88	19	7	57	155
07/69	287425	91	16	6	55	152
08/69	299100	85	16	6	55	155
09/69	206800	83	15	6	61	142
10/69	181000	83	17	6	61	122
11/69	205100	90	16	6	60	118
12/69	276900	76	16	5	52	114
01/70	186350	66	15	5	54	116
02/70	152100	58	15	5	41	122
03/70	153730	59	13	5	39	125
04/70	45700	54	13	5	37	109
05/70	0	51	14	5	29	94
06/70	0	47	14	3	18	84
07/70	0	44	11	2	16	74
08/70	0	40	9	1	14	63
09/70	0	40	7	1	13	43
10/70	0	34	6	1	14	37
11/70	0	30	5	1	15	35
12/70	0	25	4	1	13	30
01/71	0	23	4	1	14	28
02/71	0	23	4	1	14	28
03/71	0	23	4	1	14	28
04/71	0	23	4	1	14	28
05/71	0	23	4	1	14	28
06/71	0	28	4	1	14	28
07/71	0	29	4	1	14	28
08/71	0	29	4	1	14	28
09/71	0	29	4	1	14	28
10/71	0	29	4	1	14	28

Table VIII-2

EXPOSURE INDEX CATEGORIZATION

Occupational Group	Exposure Category	Effective Herbicide Orange Gallons Corresponding to Exposure Category	Number of Ranch Hand Participants in Exposure Category
Officer	Low	≤ 35,000	140
	Med	35,000 - 70,000	150
	High	> 70,000	151
Enlisted-Flying	Low	≤ 50,000	67
	Med	50,000 - 85,000	70
	High	> 85,000	66
Enlisted-Ground	Low	≤ 20,000	185
	Med	20,000 - 27,000	186
	High	> 27,000	207

Chapter IX

GENERAL PHYSICAL HEALTH

Five general variables were used in the analyses of the general health status of the study participants. The individual's self-perception of health was obtained during questionnaire administration and reflects a personal and subjective evaluation of health. It is susceptible to varying degrees of bias, both conscious and subconscious. The physician's assessment of the presence of distress is a crude objective measure of general health status and is less biased. This assessment was made on initial observation by the examiner, prior to any direct examination. Thus, patients who appeared ill or in distress on this initial observation were generally quite ill. The examining physician also reported his assessment of the concordance between the subject's apparent age and his chronological age. Two other variables, percent body fat and the erythrocyte sedimentation rate, were also evaluated. There were 1045 Ranch Hand and 773 originally selected comparison participants included in the analyses in this chapter. Slight variations in these numbers occur occasionally due to missing data. Similar analyses were conducted using all compliant comparisons, regardless of replacement status. The results of these additional analyses were essentially no different from the results of the analyses with the originally selected comparisons presented in this chapter. Appendix IX contains representative results of these additional analyses. The relative risks and confidence intervals for the dependent variables analyzed in this chapter are included in Appendix XVIII.

1. Subjective Assessments

The results of a log-linear analysis of the self-perception of health in the Ranch Hand and comparison groups with three covariates (age, race and occupational category) are discussed in this section and are shown in Table IX-1.

Table IX-1

SELF-PERCEPTION OF HEALTH BY GROUP AND AGE

Age	Perception	Ranch Hand Number	Ranch Hand Percent	Comparisons Number	Comparisons Percent	P value
≤40	Excellent	129	(34.5)	91	(38.6)	
	Good	173	(46.3)	120	(50.8)	
	Fair/Poor	72	(20.9)	25	(10.6)	P=.017*
>40	Excellent	254	(39.1)	203	(38.7)	
	Good	256	(39.4)	239	(45.5)	
	Fair/Poor	139	(21.4)	83	(15.8)	P=.025**

*Relative risk ≤40 = 1.82; 95% Confidence Interval (1.18 to 2.10)
**Relative risk >40 = 1.35; 95% Confidence Interval (1.05 to 1.76)

This analysis demonstrates a statistically significant difference between the two groups, with the Ranch Handers perceiving their health to be poorer than the comparisons. No significant three-factor interaction effects associated with self-perception and group were observed. However, age had a statistically significant association with health perception ($P < 0.001$) and with group membership ($P = 0.02$), thus indicating confounding by age. Race was found to have no association with either group membership or perception of health (P values of 0.94 and 0.87, respectively).

The examiner's initial assessment of the appearance of ill health or distress also paralleled the participants' self-perceptions, with more Ranch Handers appearing to be ill than comparison subjects. Although these ill-appearing individuals accounted for less than 1% of each group, there was borderline statistical significance as shown in Table IX-2.

Table IX-2

EXAMINER'S ASSESSMENT OF ILLNESS OR DISTRESS BY GROUP

Examiner's	Ranch Hand		Comparison	
Assessment	Number	Percent	Number	Percent
Ill	8	(0.8)	1	(0.1)
Well	1,033	(99.2)	769	(99.9)

$P = 0.056$

This measure is somewhat more objective than the participant's self-perception of health but is nevertheless influenced by the participant's emotional status, and bias can thus still be a factor in this result. The participants' self-perception of health appeared to be worse than the examiner's assessment in both groups; however, as demonstrated in Table IX-3, the pattern of discordance does not differ between the two groups. When the examiner's estimates of the participant's apparent ages were contrasted to their chronological ages, 976 (93.4%) of the Ranch Handers and 737 (95.6%) of the comparisons were observed to appear as old as they actually were. Fifty-one (4.9%) of the Ranch Handers and 19 (2.5%) of the comparisons appeared to be younger than their actual age while 18 (1.7%) and 15 (2.0%) respectively appeared to be older. This observation was statistically significant ($P = 0.029$) and demonstrated a tendency for the Ranch Handers to appear somewhat younger than their actual ages.

Table IX-3

DISCORDANT SELF-PERCEPTIONS OF HEALTH

	Better than Examiner	Worse than Examiner
Ranch Hand	2	205
Comparison	0	109

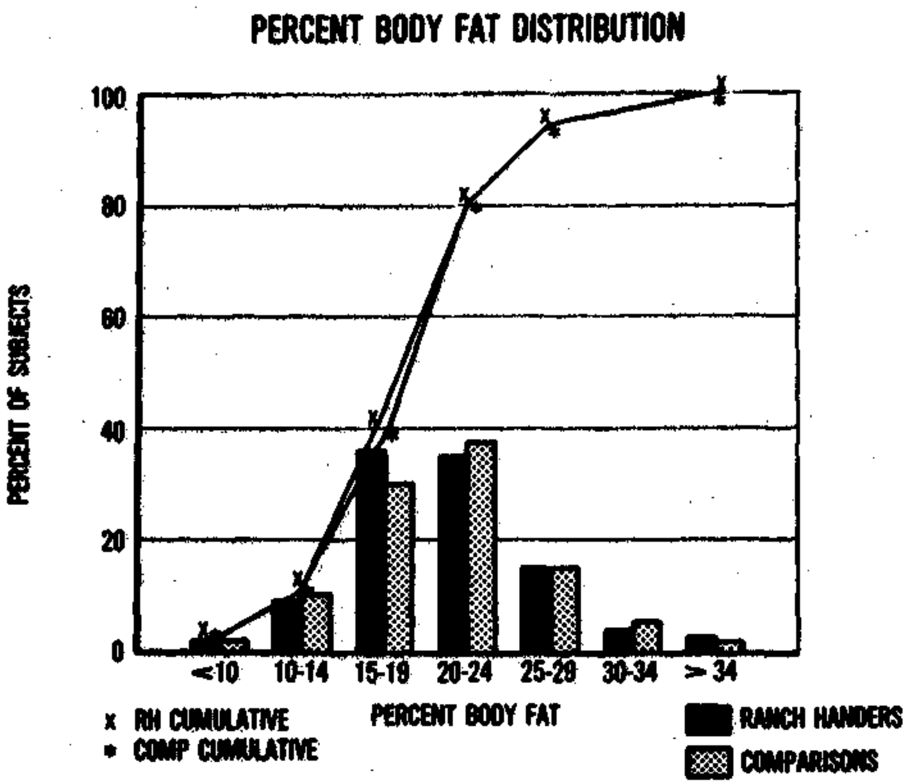
2. Objective Assessments

Percent body fat and erythrocyte sedimentation rate were also analyzed in the setting of general health status. While these measures are not indicative of specific diseases, they do indirectly reflect the general state of health. Body fat percentages were calculated from height (inches) and weight (lbs) measurements (Hodgdon, 1983) using the formula.

$$\% \text{ Body Fat} = (\text{weight}/\text{height}^2)\ (1015.724) - (17.28460).$$

Data were missing or unmeasurable (greater than 100%) for 7 participants (3 comparison and 4 Ranch Handers), and these individuals were excluded from the analysis. The distribution of these data is shown in Table IX-4 and Figure IX-1, where the percentage of participants falling in each grouping and the cumulative percentages are displayed.

Figure IX-1



The percent of body fat appeared to be reasonably normal in its distribution. No significant differences were detected between the variances (P = 0.34) or the means (P = 0.67) of the two groups.

Table IX-4

DESCRIPTIVE STATISTICS - PERCENT BODY FAT

	Number of Subjects	Mean	Std Dev
Ranch Hand	1,041	21.12	5.36
Comparison	770	21.22	5.19

In an effort to assess the extremes of obesity and leanness in the two groups of participants, individuals below 10% or over 25% body fat were considered to be lean or obese, respectively. The distribution of subjects in three weight categories is shown in Table IX-5. Chi-square procedures revealed no significant differences between the Ranch Hand and comparison groups (P=0.89).

Table IX-5

DISTRIBUTION OF BODY FAT PERCENT

	Lean <10%)		Normal (10-25%)		Obese (>25)		
	Number	Percent	Number	Percent	Number	Percent	Total
Ranch Hand	13	(1)	824	(79)	207	(20)	1044
Comparison	7	(1)	607	(79)	157	(20)	771

P= 0.89

The percent body fat and group membership relationship was further evaluated by covariance analysis using age, race and occupational category as covariates. Age and percent body fat were associated (P = 0.02), but this association was not affected by group membership; that is, there was no three-way interaction (P = 0.17). None of the sources of variation associated with race were found to be significant. Percent body fat was significantly different between the three occupational categories (P = 0.04), but this association was the same in both Ranch Hand and comparison groups.

Sedimentation rate values presented a right skewed distribution for both groups. Table IX-6 presents the percentile values for each group. A two-sample Kolmogorov-Smirnov test revealed no significant differences in the two unadjusted distributions (P = 0.99). The normal range of sedimentation rate for males is less than or equal to 12 mm and only 5% of each group exceeded normal.

Table IX-6

PERCENTILE DISTRIBUTION OF SEDIMENTATION RATE RESULTS

	5%	25%	50%	75%	95%
Ranch Hand	0	1	2	4	12
Comparison	0	1	2	4	13

Kolmogorov-Smirnov; P = 0.99

A multifactor log linear analysis of sedimentation rate by group membership, age (≤40, >40), hematocrit (<42, 42-52, or >52%) and the examiner's assessment of illness or distress was performed. The interaction of sedimentation rate, group membership, and age was significant (P = 0.002) as shown in Table IX-7. Ranch Handers 40-years of age or less had significantly fewer sedimentation rate abnormalities than did their comparisons, while no group difference was noted in individuals over the age of 40.

Table IX-7

SEDIMENTATION RATE, AGE AND GROUP MEMBERSHIP

		Sedimentation Rate				
		Abnormal		Normal		
Age	Group	Number	Percent	Number	Percent	P Value
≤ 40	Ranch Hand	2	(0.5)	372	(99.5)	0.001
	Comparison	10	(4.2)	227	(95.8)	
> 40	Ranch Hand	39	(5.8)	628	(94.2)	0.764
	Comparison	29	(5.4)	504	(94.6)	

The sedimentation rate was found to have a significant association with hematocrit, the appearance of illness or distress, and percent body fat. Table IX-8 displays these data. Since these variables were unassociated with group membership, combined data for both groups are used.

Table IX-8

SEDIMENTATION RATE HEMATOCRIT/DISTRESS/BODY FAT ASSOCIATIONS

	Sedimentation Rate				
	Abnormal		Normal		
	Number	(Percent)	Number	(Percent)	P Value
	Hematocrit				
< 42%	13	(11.3)	102	(88.7)	
42-52%	66	(4.0)	1598	(96.0)	<0.001
> 52%	1	(3.1)	31	(96.9)	
Appearance of Illness or Distress					
Ill	2	(22.2)	7	(87.8)	0.009
Well	78	(4.3)	1724	(95.7)	
% Body Fat					
< 10	3	(15.0)	17	(85.0)	
10-25	59	(4.1)	1372	(95.9)	0.049
> 25	19	(5.2)	348	(94.8)	

These findings are consistent since an increasing sedimentation rate, abnormal body weight, decreasing hematocrit, and an ill appearance are all traditional indicators of illness, and therefore should be related.

The relationships between self-perception of health, sedimentation rate, and age were also explored. These significant relationships are shown in Table IX-9.

Table IX-9

SELF-PERCEPTION OF HEALTH, AGE/SEDIMENTATION RATE ASSOCIATIONS

	Self-Perception of Health			
	Excellent	Good	Fair/Poor	P Value
Sedimentation Rate				
Abnormal	18	35	28	<0.001
Normal	671	765	294	
Age				
≤ 40	224	294	97	
> 40	465	506	225	0.06

These relationships were independent of group membership and are not unusual since illness generally increases with advancing age.

3. Herbicide Exposure Analysis

The exposure index was applied to the variables in the general health analysis to determine whether a dose-response effect could be identified. As described in Chapter VIII, the index is expressed in equivalent-gallons of dioxin-containing herbicide potentially encountered by each individual during his Ranch Hand tour of duty. Three categories of exposure were used: low, medium, and high. The cutoff values for these categories were chosen so that statistical power could be maximized in the analyses.

The interrelationship between a Ranch Hander's self-perception of health and exposure is shown in Table IX-10. Three occupational groupings were analyzed: officers, flying enlisted, and enlisted ground personnel. Nonflying officers were included in the analysis and were assigned to the low exposure category. Their jobs were primarily administrative in nature and involved relatively lower levels of exposure than the flying officers.

Table IX-10

HEALTH PERCEPTION IN RANCH HANDERS BY OCCUPATIONAL GROUP AND EXPOSURE CATEGORY

Occupational Group	Perception	Counts Within Exposure Category: Low	Med	High	P Value
Officer	Excellent	65	65	68	
N = 361	Good	34	45	42	0.72
	Fair/Poor	11	18	13	
Enlisted, flying	Excellent	18	18	23	
N = 183	Good	29	24	29	0.84
	Fair/Poor	12	16	14	
Enlisted, ground	Excellent	43	41	41	
N = 472	Good	59	95	67	0.13
	Fair/Poor	48	42	36	
Total: 1016					

These analyses revealed no significant association between exposure and perception of health. The P value of 0.13 among the enlisted ground personnel is of interest, but consistent trends are not seen in the data. Similarly, exposure was found to have no significant association with the examiner's assessment of distress or ill health. The occupational category analysis is shown in Table IX-11. Statistical testing of these data was not conducted due to the small number of individuals judged to be ill by the examining physician.

Table IX-11

EXAMINER'S ASSESSMENT OF HEALTH IN RANCH HANDERS
BY OCCUPATIONAL GROUP AND EXPOSURE CATEGORY

Occupational Group	Illness or Distress	Counts Within Exposure Category Low	Med	High
Officer	Ill	0	1	1
	Well	111	127	124
Enlisted, flying	Ill	0	0	1
	Well	59	59	65
Enlisted, ground	Ill	2	0	3
	Well	149	178	142

Similarly, the associations between exposure and apparent age and exposure and body fat were evaluated. These data are presented in Tables IX-12 and IX-13.

Table IX-12

APPARENT AGE OF RANCH HANDERS BY OCCUPATIONAL GROUP
AND EXPOSURE CATEGORY

Occupational Group	Apparent Age	Counts Within Exposure Category Low	Med	High	P Value
Officer					
	Younger	7	10	8	0.99
	Same	103	117	116	
	Older	1	1	1	
Enlisted-flying					
	Younger	1	5	2	
	Same	57	54	64	0.22
	Older	1	0	0	
Enlisted-ground					
	Younger	5	6	6	
	Same	142	169	136	0.88
	Older	4	4	6	

Table IX-13

PERCENT BODY FAT BY OCCUPATIONAL GROUP
AND EXPOSURE CATEGORY

Occupational Group	% Body Fat	Counts Within Exposure Category Low	Med	High	P Value
Officer					
	≤10%	0	1	1	
	10-25%	91	97	103	0.57
	≥25%	20	30	21	
Enlisted-flying					
	≤10%	1	1	0	
	10-15%	48	52	51	0.34
	≥25%	10	6	15	
Enlisted-ground					
	≤10%	2	4	3	
	10-25%	114	136	115	0.95
	≥25%	35	39	30	

It is evident from these data that levels of exposure had no relationship to the examiner's assessment of apparent age and percent body fat regardless of occupational category.

4. Summary

Overall, the analyses of the general physical health of the study participants revealed classical associations between clinical measures of ill health such as sedimentation rate, obesity/leanness, age, hematocrit, self-perception and the appearance of distress. Statistically significant group differences between the Ranch Hand and Comparison groups were limited to the subjective measures of self-perception of health and the examiner's assessment of illness or distress. The Ranch Handers, as a group, perceived themselves to be in poorer health than did the comparison group. Similarly, the examiner felt that more Ranch Handers appeared ill than did the comparisons. However, ill appearing individuals accounted for less than 1% of both groups. The analysis of these variables against the exposure index did not reveal any dose-response effects. Overall, the available evidence does not support the presence of such an herbicide effect operating at this time.

Chapter X

MALIGNANCY

1. Introduction

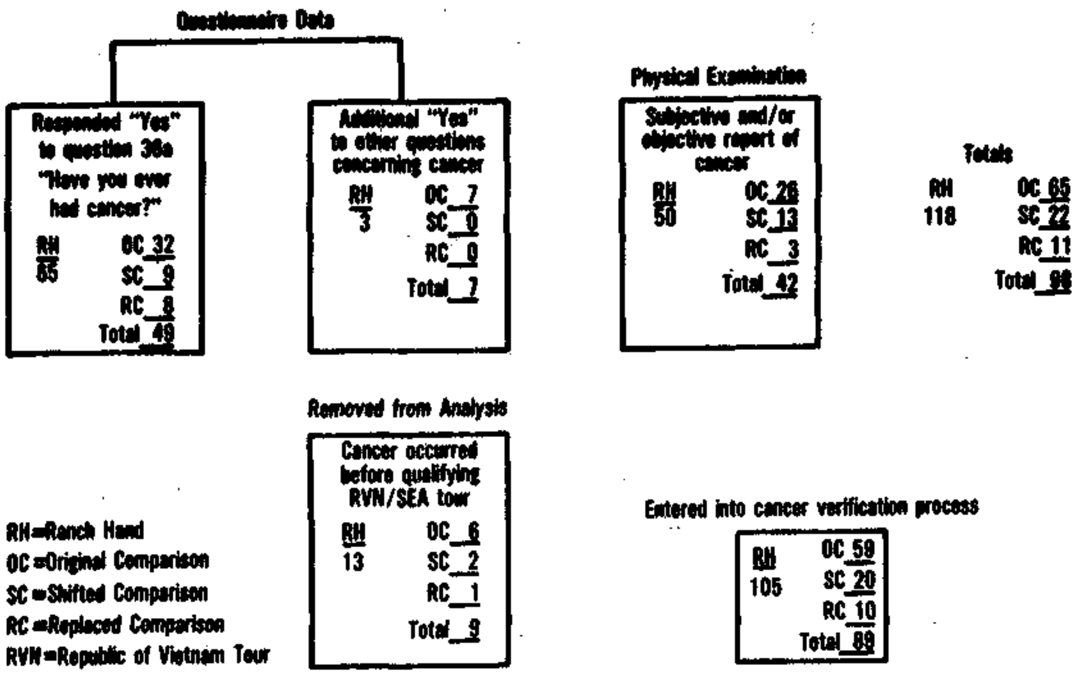
Of all the health effects being attributed to dioxin, cancer is one of the most feared in the minds of the veteran groups, the media and the general public. Dioxin has been identified as a carcinogen or cocarcinogen in some strains of rats and mice (Toth, et al, 1979; Kociba et al, 1978, 1979; Kouri, 1978); however, its carcinogenic effects in humans are unclear. Epidemiologic studies of carcinogenic effects in humans have been generally limited to investigations of phenoxy herbicide exposure among soft-tissue sarcoma patients in Sweden (Hardell and Sandstrom 1979; Axelson, 1977) and studies among industrial groups involved in the production of trichlorophenol and 2,4,5-T (Zack, 1980; Honchar, 1981). These studies have been contradictory and the issue is still being debated in scientific as well as public forums. The clarification of this important issue is a major focus of the Air Force Health Study.

Questions concerning a history of cancer or tumor were asked during both the in-person questionnaire and the physical examination. Question 36a of the study subject questionnaire concerned cancer alone while other areas of the questionnaire focused on tumors or other major medical conditions. In addition, the physical examination subjectively identified additional participants with a history of cancer in the past medical history and objectively identified participants with evidence of prior or newly diagnosed cancer. Figure X-1 shows the algorithm used for data collection for cancer in the study population, as well as those reported cancers that were entered into the cancer verification process.

In this algorithm 114 individuals (65 Ranch Handers and 49 comparisons responded "yes" to question 36a, 10 other individuals (3 Ranch Handers and 7 comparisons) responded yes to other questionnaire questions concerning tumors or other major conditions, while 92 additional individuals (50 Ranch Handers and 42 comparisons) reported or were diagnosed as having cancer or tumors during the physical examination. A total of 22 reported cancers occurred prior to the individual's Southeast Asia tour of duty, and these cancers were removed from all analyses. A total of 194 individuals reporting cancer were entered into the verification process (105 Ranch Handers and 89 comparisons).

Cancer verification was completed by review of the individual's medical records and available pathology reports. Although cancers reported by all participants were entered into the validation process, only the data from the Ranch Hand group and the subset of originally selected comparisons who completed physical examination were fully analyzed statistically. The rationale

Figure X-1
ALGORITHM OF COUNTS ON REPORTED CANCERS BY SOURCE OF DATA



for this restriction of the database is discussed in Chapter V, Study Selection and Participation Bias. Verification records were obtained with permission forms signed by the participants at the time the questionnaire was administered. The verification process was supported with a limited access computer software program. All reported cancers were classified as to behavior, type and morphology. In addition, cancers were classified as being skin or systemic due to the differing natures of these disease processes. The findings of the verification process are presented in Table X-1.

Table X-1

SUMMARY OF CANCER VERIFICATION PROCESS

Location	Behavior of Cancer	Ranch Hand	Comparison* O	Comparison* S	Comparison* R	Comparison* Total
Skin	Malignant	35	15	7	5	27
	Benign	17	14	3	1	18
	Diagnosis not supported	13	6	4	1	11
	Differential Diagnosis at physical examination; individual declined follow-up	13	3	3	0	6
	No record of treatment at facility as reported	1	1	0	0	1
	Medical record not available	0	0	1	1	2
	TOTAL	79	39	18	8	65
Systemic	Malignant	14*	10	2*	2	14
	Benign	8	10	0	0	10
	Not supported	4	0	0	0	0
	Medical record not available	0	0	0	0	0
	TOTAL	26	20	2	2	24

*Includes 1 Ranch Hander and 1 comparison who expired following interview

O = Original
S = Shifted
R = Replacement

2. Skin Cancer

Seventy-five percent (79/105) of all Ranch Hand and 73% (65/89) of all comparison-reported and verified neoplasms were cancer of the skin. Forty-four percent (35/79) of the Ranch Hand reported skin cancers were verified as malignant while 42% (27/65) of the reported total comparison skin cancers were verified as malignant (P = 0.74). All individuals with malignant skin cancer were non-Black. The occurrence of verified skin cancer in those participants who completed the questionnaire (regardless of their compliance to physical examination) was significantly higher in the Ranch Hand group when compared to the total comparison group (P=0.03) or to the subset of original comparisons (P=0.04). Table X-2 shows the distribution of verified malignant skin cancers by cell type.

Table X-2

VERIFIED MALIGNANT SKIN CANCERS BY CELL TYPE;
REPORTED BY FULLY AND PARTIALLY COMPLIANT PARTICIPANTS

Cell Type	Ranch Handers*	Comparisons O	Comparisons S	Comparisons R	Comparisons Total
Basal Cell	31	11	5	5	21
Melanoma	3	1	1	0	2
Squamous Cell	1	3	0	0	3
Fibrosarcoma	0	0	1	0	1
TOTAL	35	15	7	5	27

*1 Ranch Hander experienced 2 skin cancers, 1 melanoma and 1 squamous cell. He has been counted only once and placed under melanoma in this table.

O = Original
S = Shifted
R = Replacement

Nonmelanoma cancer accounts for 91% (32/35) of the Ranch Hand and 93% (25/27) of the comparison group skin cancers. This difference is not statistically significant (P = 0.87). These findings are consistent with reported data that nonmelanoma cancer of the skin is the most common malignant neoplasm in the white population of the United States (Schottenfeld and Fraumeni, 1982). The distribution of these verified skin cancers by anatomic site is presented in Table X-3.

Table X-3

COUNTS OF SKIN CANCER BY ANATOMIC SITE

	Nonmelanoma skin cancer					Melanoma				
		Comparison					Comparison			
	RH	O	S	R	Total	RH	O	S	R	Total
Face, head and neck	26	12*	5**	3	20	1	0	0	0	0
Upper extremities	1	1	1	0	2	0	1	0	0	1
Trunk	5+	1	0	2	3	2	0	1	0	1
Lower extremities	0	0	0	0	0	0	0	0	0	0
TOTAL	32	14	6	5	25	3	1	1	0	2

+Includes 1 Squamous cell
*Includes 3 squamous cell
**Includes 1 fibrosarcoma

RH = Ranch Hand
O = Original
S = Shifted
R = Replacement

Nonmelanoma skin cancers arose on the face, head and neck in 81% (26/32) of the Ranch Handers and in 80% (20/25) of all comparisons (P = 0.91). This distribution and the cell types of skin cancers is consistent with recently published information on the epidemiology of skin cancer (Schottenfeld and Fraumeni 1982). The occupational category of those individuals with verified skin cancer are presented in Table X-4. The counts of these individuals with cancer are relatively small and all occupational categories contribute to the Ranch Hand increase. Followup reports will contain additional analyses of these data with detailed considerations of sample size and age in each of the occupational strata.

Table X-4

COUNTS OF THE FACE, HEAD, AND NECK DISTRIBUTION OF NONMELANOMA SKIN CANER; RANCH HAND VERSUS TOTAL COMPARISONS

	Ranch Hand		Total Comparisons	
Occupational Code	Cases	Rate/100	Cases	Rate/100
Officers	16	3.7	11	1.9
Flying Enlisted	3	1.5	1	0.4
Nonflying Enlisted	7	1.3	8	1.1
	26		20	

While medical literature implicates ultraviolet radiation from the sun as the dominant risk factor in the development of nonmelanomic skin cancer (Scott et al 1974), it was not possible to fully evaluate the effects of sun exposure in the initial phase of this study. Information required for this analysis will be obtained in the follow-up phases of the effort.

3. Systemic Cancer

A total of 50 systemic cancers (26 Ranch Handers and 24 comparisons) were reported and entered into the verification process (Table X-1). Of these, 14 Ranch Handers and 14 comparisons (10 Originals, 2 Shifted, and 2 Replacements) were verified as having had malignant systemic neoplasms. All individuals with systemic malignancy are non-Black.The site specific classification of these neoplasms is presented in Table X-5.

Table X-5

MORBIDITY SITE SPECIFIC VERIFIED SYSTEMIC MALIGNANT NEOPLASMS

Site: ICD Code (9th Ed)	Ranch Hand	Comparison O	Comparison S	Comparison R	Comparison Total
Lip, oral cavity, pharynx (140-149)	4	2	0	0	2
Digestive organ, peritoneum (150-159)	-	4	0	1	5
Respiratory, intrathoracic (160-165)	3*	1	1*	0	2
Bone, connective tissue, skin, breast (170-175)	-	-	-	-	-
Genitourinary organ (179-189)	6	2	1	0	3
Other & unspecified sites (190-199)	1	1	0	0	1
Lymphatic & hematopoietic tissue (200-208)	-	0	0	1	1
TOTAL	14	10	2	2	14

*Includes 1 Ranch Hander and 1 comparison who expired following interview

O = Original
S = Shifted
R = Replaced

Four Ranch Handers and 2 original comparisons were found to have had neoplasms of the lip, oral cavity and pharynx, and all of these individuals reported a history of cigarette and/or cigar smoking.

Six Ranch Handers and 3 comparisons were found to have had malignancies of the genitourinary organs. The 6 Ranch Hand cancers included 1 prostate, 2 testicular, 2 bladder and 1 kidney neoplasm while the 3 comparison cancers included 1 of the prostate and 2 of the bladder. Both cases of testicular cancer were of a germ-cell morphology (one embryonal and one seminoma). Unadjusted statistical testing revealed no significant difference in total genitourinary cancer in the two groups ($P = 0.42$). Peak incidence rates of testicular cancer in the general population occur between the ages of 35 and 55, and bladder cancer has a peak age of onset between 50 and 70 years. All Ranch Hand bladder cancers occurred prior to age 50 and all verified comparison genitourinary cancer occurred at age 55 or later. The Ranch Hand testicular cancers occurred at 35 and 38 years of age. These are observational data, and are based on very small sample size.

Five comparisons were found to have had verified malignancies of the digestive organs. There were no Ranch Hand cancers of this organ system. These cancers included 1 of the appendix, 1 of the pancreas, and 3 colon cancers. The annual incidence rate for colon cancer increases dramatically with increasing age after the age of 30. The ages at the onset of the colon cancers in the comparison group were 35, 43, and 50 years. The occurence of gentourinary, oropharyngeal and digestive cancers in the study population was compared to the experience of the Surveillance, Epidemiology and End Results program (SEER). Based on these tumor registry data, there is a 30% probability of observing two or more testicular cancer in the Ranch Hand group, and a 29% probability of two or more bladder cancers. Similar contrasts revealed only a 3% chance of observing the 4 oropharyngeal cancers and a 2% chance of seeing a total absence of digestive cancers in the Ranch Hand group. The probabilities of finding the observed numbers of these malignancies in the comparison group were 32% or greater.

Table X-6 shows the known morbidity and mortality of the Ranch Handers and comparisons from cancer to date. Appendix VIII shows the site specific distribution of both the morbidity and mortality study cancers. The mortality sections of these tables include only the first cohort of the comparison population from the Baseline Mortality Study (Lathrop, 1983).

Table X-6

TOTAL MORTALITY AND MORBIDITY STUDY
MORPHOLOGY OF SYSTEMIC NEOPLASM

ICD-O CODES	NOMENCLATURE	MORTALITY RANCH HAND	MORTALITY COMPARISON	MORBIDITY* RANCH HAND	MORBIDITY* COMPARISON O	MORBIDITY* COMPARISON S	MORBIDITY* COMPARISON R
M800	Neoplasm not otherwise specified (NOS)						
	Bronchus and Lung	0	1	0	0	0	0
	Intestinal Tract	0	1	0	0	0	0
M801-804	Epithelial neoplasms						
	Appendix	0	0	0	1	0	0
	Bladder	0	0	0	1	0	0
	Bronchus and Lung	1	1	1	0	0	0
	Kidney	1	0	0	0	0	0
	Lip	0	0	1	0	0	0
	Nasopharynx	0	1	0	0	0	0
	Tongue	0	0	1	0	0	0
	Unspecified site	1	1	0	0	0	0
	Vocal Cord	0	0	0	1	0	0
M805-808	Papillary and Squamous Cell						
	Lip	0	0	2	2	0	0
	Lung	0	0	1	0	0	0
M812-813	Transitional Cell Papillomas and Carcinomas						
	Bladder	0	0	2	0	1	0
M814-838	Andenomas and Adenocarcinomas						
	Bronchus and Lung	0	1	0	0	0	0
	Colon	0	0	0	2	0	1
	Kidney	0	1	1	0	0	0
	Prostate	0	0	1	1	0	0
	Pancreas	0	0	0	1	0	0
M850-854	Ductal, lobular, and medullary neoplasms						
	Thyroid	0	0	0	1	0	0
M872-879	Nevi and melanomas						
	Mediastinal	1	0	0	0	0	0
M905	Mesothelioma						
	Bronchus and Lung	0	1	0	0	0	0
M906-909	Germ cell neoplasms						
	Testicle	0	0	2	0	0	0
M938-948	Gliomas						
	Frontal Lobe	0	1	1	0	0	0

Table X-6 (Cont)

TOTAL MORTALITY AND MORBIDITY STUDY
MORPHOLOGY OF SYSTEMIC NEOPLASM

ICD-O CODES	NOMENCLATURE	MORTALITY RANCH HAND	MORTALITY COMPARISON	MORBIDITY* RANCH HAND	MORBIDITY* COMPARISON O	S	R
M965-966	Hodgkins disease Hodgkins (NOS)	0	0	0	0	0	1
M986	Myeloid Leukemias Acute myelocytic leukemia	0	1	0	0	0	0
		4	10	13	10	1	2

O = Original
S = Shifted
R = Replaced

*Two morbidity study participants (1 Ranch Hand, 1 comparison) expired following interview. They are included in the mortality column of this Table because of their date of death.

4. Covariate Analysis

Group Membership

The previous sections of this chapter contained descriptions of the cancer data on the occurrence of skin cancer and systemic cancer in the Ranch Hand and originally selected comparison groups. Except where noted, the remaining analyses in this chapter are based on the Ranch Hand and comparison population that had verified cancer and had completed the physical examination. Covariates used in these analyses included smoking habits and exposure to asbestos, industrial chemicals (yes, no), insecticides (yes, no), degreasing chemicals (yes, no), and nonmedical x-ray sources (yes, no). The results of the basic two-factor analysis are shown in Table X-7.

Table X-7

VERIFIED CANCER AND GROUP MEMBERSHIP

		Original Comparisons (N=773)		Ranch Hand (N=1045)		Total Comparisons* (N=1194)	
Skin Cancer	Yes	11		35		25	14
	No	762		1010		1169	407
			P = <0.01		P = 0.07		
Systemic Cancer	Yes	8		13		11	
	No	765		1032		1183	
			P = 0.68		P = 0.46		

* This total does not include the 30 participants interviewed by USAF interviewers.

The group differences in skin cancer are statistically significant, in the original subset that completed physical examination, (P = < 0.01) and borderline in the total comparisons (P = 0.07), with an excess in the Ranch Hand group. The relative odds of skin cancer in the Ranch Handers are 2.35 and are 1.20 for systemic cancer, with confidence intervals of 1.16 to 4.90, and 0.47 to 3.15 respectively. These broad intervals are due to the small numbers of cancers available for analysis.

The analysis of skin cancer in the Ranch Handers and the original comparisons was repeated with months of agricultural/forestry/fisheries work as a covariable. Seventy-one (6.8%) of the Ranch Handers and 66 (8.5%) of the original comparisons had worked in these occupations; however, these statistical adjustments did not alter the significant difference between the groups. The P value after adjustment remained 0.01. These analyses are as yet incomplete since they have not accounted for the relationship between skin cancer and geographic area of residence or exposure to other potential skin carinogens. Geographic area of current residence in a mobile military population may not discriminate differences in ultraviolet radiation exposure. An attempt to collect data that will support analyses for geographic and ethnic background will be made at the time of the first follow-up examination.

Three-factor analytic techniques were used to account for the possible confounding effects of the covariables listed above. Exposure to industrial chemicals, degreasing chemicals and smoking habits were not different in the Ranch Hand and comparison groups. The analyses of systemic cancer demonstrated an association between cancer and smoking which approached statistical significance (P = 0.07). However, there were no significant differences or suggestive trends between the groups for systemic cancer.

Significant group differential in exposure to x-ray ($P < 0.001$), insecticides ($P < 0.001$), and asbestos ($P = 0.05$) were also identified. More comparisons than Ranch Handers were exposed to asbestos and x-ray but more Ranch Handers had previously been exposed to insecticides, many during their tours of duty in RVN. Three-way interactions between variables were significant only for the systemic cancer by group by insecticide analysis ($P = 0.01$) and suggestive for the systemic cancer by asbestos by group analysis ($P = 0.16$). The results of these analyses are displayed in Table X-8.

Table X-8

RESULTS OF THREE-FACTOR LOG-LINEAR ANALYSES OF SYSTEMIC CANCER, GROUP MEMBERSHIP AND CHEMICAL EXPOSURE (P VALUES)

Exposure	Statistical Relationship			
	Group by Cancer	Group by Exposure	Cancer by Exposure	Cancer by Exposure by Group
Asbestos	0.72	0.04	0.33	0.16
Degreasing Chemicals	0.68	0.33	0.71	0.23
Industrial Chemicals	0.71	0.25	0.34	0.84
Insecticides	0.72	<0.001	0.89	0.01
Smoking	0.50	0.46	0.07	0.53
X-Ray	0.63	<0.001	0.46	0.86

Table X-9

RESULTS OF THREE-FACTOR LOG-LINEAR ANALYSES OF SKIN CANCER, GROUP MEMBERSHIP AND EXPOSURE (P VALUES)

Exposure	Analysis			
	Group by Cancer	Group by Exposure	Cancer by Exposure	Cancer by Exposure by Group
Asbestos	0.009	0.04	0.24	0.11
Degreasing Chemicals	0.009	0.37	0.20	0.47
Industrial Chemicals	0.009	0.30	0.03	0.58
Insecticides	0.02	<0.001	0.19	0.79
Smoking	0.01	0.44	0.70	0.22
X-Ray	0.008	<0.001	0.86	0.51

As shown in Table X-9, analyses of skin cancers demonstrated a significant difference between the Ranch Hand and the original comparison group that completed physical examination. These data again demonstrate the significant group differential in skin cancer. Even after covariate adjustment (asbestos, industrial chemicals, smoking, x-ray, insecticide and degreasing chemical exposure) the significant group difference in the occurrence of skin cancer remained. Significant between group differentials were noted for x-ray and, asbestos exposure, as previously seen in the systemic cancer analyses. A significant association between skin cancer and exposure to industrial chemicals was found (P = 0.03). Associations between the occurrence of skin cancer and exposure to degreasing chemicals and insecticides are also of interest, with suggestive P values of 0.20 and 0.19 respectively.

5. Exposure Index Analyses

The group difference in cancer occurrence was further evaluated using the exposure index, divided into low, medium, and high degrees of exposure. These analyses used only data gathered on the Ranch Hand group. Table X-10 contains the data and results from the basic two-factor analysis (herbicide exposure versus cancer).

Table X-10

HERBICIDE EXPOSURE VERSUS CANCER

Occupational Group	Exposure Level	Systemic Cancer Yes	Systemic Cancer No	Skin Cancer Yes	Skin Cancer No
Flying Officers					
	Low	1	110	7	104
	Medium	1	127	5	123
	High	3	122	8	117
		P = 0.48		P = 0.62	
Flying Enlisted					
	Low	0	59	3	56
	Medium	2	57	1	58
	High	1	65	0	66
		P = 0.35		P = 0.14	
Ground Enlisted					
	Low	2	149	2	149
	Medium	3	176	5	174
	High	0	148	4	144
		P = 0.31		P = 0.63	

These analyses did not reveal a dose-response effect between herbicide exposure and the occurrence of either skin or systemic cancer in the Ranch Hand group; however, the number of cancers within each exposure level are very small. A "suggestive" negative association between herbicide exposure and skin cancer was noted among the enlisted flying group (P = 0.14) with decreasing occurrence of cancer with increasing exposure; however, cell sizes were quite small. Three-factor analysis suggested the presence of interactive effects from insecticide and x-ray exposure, in the flying officers for systemic cancer, and industrial chemicals, degreasing chemicals, and insecticides among the enlisted ground personnel for skin cancer. The results of these analyses are shown in Tables X-11, and X-12, X-13, X-14, and X-15.

Table X-11

THREE-FACTOR ANALYSIS: EXPOSURE, SYSTEMIC CANCER, AND INSECTICIDE EXPOSURE AMONG FLYING OFFICERS*

Insecticide Exposure	Herbicide Exposure	Systemic Cancer Yes	Systemic Cancer No
Yes	low	1	74
	medium	1	79
	high	0	72
		P = 0.62	
No	low	0	36
	medium	0	48
	high	3	50
		P = 0.09	

* Three-way interaction P value = 0.10

These data demonstrate confounding by insecticide exposure, with a borderline association between systemic cancer and herbicide (P = 0.09) in the noninsecticide-exposed group of officers. However, the validity of statistical testing in this instance is compromised due to the extremely small number of cases in the analysis. Similarly, this effect is seen with x-ray exposure (Table X-12).

Tables X-13, X-14 and X-15 present the data for the herbicide exposure, cancer, industrial chemical, degreasing chemical and insecticide three-factor analyses for enlisted personnel. Confounding is again seen.

Table X-12

THREE-FACTOR ANALYSES: HERBICIDE EXPOSURE, SYSTEMIC CANCER, AND X-RAY EXPOSURE AMONG FLYING OFFICERS

X-ray Exposure	Herbicide Exposure	Systemic Cancer Yes	Systemic Cancer No
Yes	low	1	23
	medium	1	23
	high	0	33
		P = 0.49	
No	low	0	87
	medium	0	104
	high	3	89
		P = 0.04	

* Three-way interaction P value = 0.04

Table X-13

THREE-FACTOR ANALYSIS: HERBICIDE EXPOSURE, SKIN CANCER, AND INDUSTRIAL CHEMICALS EXPOSURE AMONG ENLISTED GROUND PERSONNEL*

Industrial Exposure	Herbicide Exposure	Skin Cancer Yes	Skin Cancer No
Yes	low	0	79
	medium	1	96
	high	3	73
		P = 0.12	
No	low	2	70
	medium	4	78
	high	1	71
		P = 0.45	

* Three-way interaction P value = 0.10

Table X-14

THREE-FACTOR ANALYSIS: HERBICIDE EXPOSURE, SKIN CANCER, AND DEGREASING CHEMICAL EXPOSURE AMONG ENLISTED FLYING PERSONNEL*

Degreasing Chemical Exposure	Herbicide Exposure	Skin Cancer Yes	Skin Cancer No
Yes	low	3	40
	medium	0	41
	high	0	51
		P = 0.04	
No	low	0	16
	medium	1	17
	high	0	15
		P = 0.42	

* Three-way interaction P value = 0.17

Table X-15

THREE-FACTOR ANALYSIS: HERBICIDE EXPOSURE, SKIN CANCER AND INSECTICIDE EXPOSURE AMONG ENLISTED FLYING PERSONNEL*

Insecticide Exposure	Herbicide Exposure	Skin Cancer Yes	Skin Cancer No
Yes	low	3	30
	medium	0	36
	high	0	41
		P = 0.03	
No	low	0	26
	medium	1	22
	high	0	25
		P = 0.32	

* Three-way interaction P value = 0.13

While these data show some confounding for exposure to x-ray, insecticides, industrial chemicals and degreasing chemicals, stratified analysis reveals no evidence of a dose-related effect for exposure to the herbicides used by the USAF in the RVN and the occurrence of cancer. The validity of the statistical testing in the exposure index analyses is compromised by the extremely small numbers of cancers available for analysis. Therefore, any inferences based on these data must be made with caution.

6. Summary

The analysis of these data revealed significantly more skin cancer in the Ranch Hand group than in the subset of original comparisons who completed physical examination. This finding was of borderline significance in all original comparisons and in the total comparison population; however, these data are not fully corrected for exposure to the sun and other skin carcinogens. There were no significant group differences for the occurrence of systemic cancer. A small increase in oropharyngeal cancers and a total absence of digestive cancers were observed in the Ranch Hand group. The exposure index analyses did not demonstrate a dose-response effect for either skin or systemic cancer. Of interest was a borderline significant association between systemic cancer and smoking in both groups, demonstrating the sensitivity of the analyses to the effects of this known carcinogen.

Chapter XI

FERTILITY AND REPRODUCTIVE OUTCOMES

1. Introduction

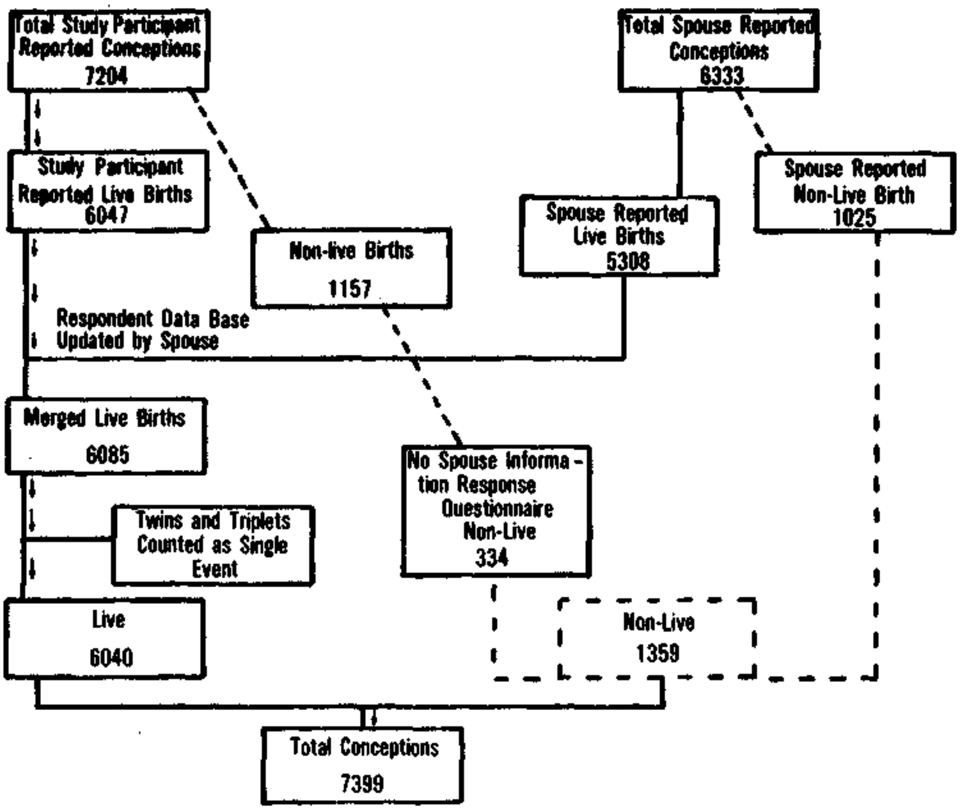
The potential effects of Herbicide Orange exposure on reproduction, fertility, or the incidence of birth defects are highly emotional issues among Vietnam veterans and have received wide media coverage. Animal fertility studies in various species have shown variations in 2,4-D; 2,4,5-T and TCDD toxicity relative to age, dosage levels and routes of administration. TCDD exposed male mice when mated with unexposed females exhibited no abnormalities in mating behavior, fertility, sperm concentration, sperm motility, survival of offspring, or neonatal development (Lamb, 1980). Conversely, administering Herbicide Orange directly to pregnant mice resulted in three fetal effects: cleft palate, decrease in fetal weight, and fetal mortality (Courtney, 1970). The Australian Birth Defects Study of veterans serving in Vietnam showed no association between birth defects of children from veterans and their Vietnam experience (Case Control Study, Australia 1983). Reports from the Seveso, Italy accident, where 220,000 people were potentially exposed to TCDD in 1976, have shown that the incidence of congenital malformations and abortions in exposed women was below expected values for the region. Of 34 aborted fetuses examined for defects, no fetal malformations were attributed to exposure to TCDD. Additionally, developmental abnormalities in children have not been exhibited (Regianni, 1980). A reproductive study of the wives of DOW Chemical Company workers exposed to 2,4,5-T/TCDD found no differences in fertility patterns, fetal wastage, or birth defects (Townsend and Badner, 1981). In 1979 the Administrator of Environmental Protection Agency declared an emergency suspension of 2,4,5,-T based on the Alsea, Oregon study finding of an increased incidence of spontaneous abortion in 3 Oregon areas sprayed with the herbicides. This study's findings prepared by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and Field Studies Division, Office of Pesticide Programs, Office of Toxic Substances, and The Environmental Protection Agency remain controversial.

Data concerning fertility and reproductive events in this study were collected during the questionnaire and physical examination. Questions regarding reproduction, fertility/infertility, and offspring history were asked of study participants both in the in-home questionnaire and at the physical examination. In addition to the data collected from male respondents, questionnaires focusing on reproductive history were administered to all available spouses and partners. The data from the reconciliation of subject and spouse questionnaire responses constitute the data base described in this report. This reconciliation was based primarily on spouse data and study participant data only when spouse data was not collected. Analyses for this chapter are based on nonverified subjective questionnaire reporting. Analyses for this chapter are based on nonverified subjective questionnaire reporting. This report also contains data on children with defects and not defects per se. When a child was reported to have multiple birth abnormalities the most serious was analyzed. Sperm counts, and sperm abnormalities from the physical examination are also analyzed. Verification of reported fertility events is presently ongoing and the analyses presented here are based on interim unverified data. Seven thousand three hundred ninety-nine conceptions are analyzed in this chapter. These represent 3293 Ranch Handers' or their spouses' reported conceptions and 4106 total comparison group or their spouses' reported conceptions. Comparison conceptions include 2669 original and 1437 shifted and replaced comparisons. The Ranch Hand and original comparisons' conceptions were analyzed considering 5 covariates: mother's smoking and drinking during each conception; mother's age; father's age; and the time of conception, i.e, before or after the father's military tour in Southeast Asia. Log-linear models were used to analyze the reproductive events of interest: miscarriages, still births, induced abortions, infant and neonatal deaths, and total numbers of live births. Live births were further analyzed for reported birth defects, learning disabilities and physical handicaps. Analyzed birth defects were those reported within a comprehensive range of ICD codes. Other reported birth defects included a broad range of pediatric conditions perceived by the parents as birth defects. Birth defects meeting ICD definition are further classified as to the severity of the defect. Fertility and reproductive outcomes were not analyzed by race for this report. These data will be presented in subsequent reports.

Questionnaire collection of fertility and reproductive information was linked to reproductive events that occurred while the participant was married, living with a partner, or reported in the questionnaire as other pregnancies. Fertility and reproductive events were keyed to the specific relationship in order to reconcile the information with similar data collected from all available spouses and partners. Figure XI-1 presents an algorithm for the development of the fertility data base.

Figure XI-1

ALGORITHM FOR THE DEVELOPMENT OF FERTILITY /REPRODUCTION DATA BASE



Of the 7204 total respondent reported conceptions shown in Figure XI-I 6047 (84%) were reported as live births and 1157 (16%) were reported as nonlive births. The spouses reported 6333 total conceptions. These are shown in the upper right portion of the figure. Of the total conceptions reported by spouses as attributable to the male respondent, 5308 (84%) were reported as live births and 1025 (16%) were reported as nonlive births. Figure XI-1 shows that the spouse-reported births were matched to the respondent reported live births and 38 children were added to the respondent data base. Six thousand eighty-five live births were thus identified. The first born of multiple births were maintained in the data base and the remaining children were deleted yielding 6040 live births. Three hundred thirty-four nonlive births were added to the nonlive birth study subject file as a result of the match of the male respondent and spouse files. Seven thousand three hundred ninety-nine total conceptions are contained in the merge of the live and nonlive birth files.

The data in Figure XI-1 are based on unverified data. The data in the fertility file has not been fully cleansed of keypunch, editing or other potential sources of errors. The study participant data collection stressed natural children; but, inadvertently, data collection resulted in information on multiple adopted, step and natural children. Additionally, there was no data link between spouse, male respondent and children. Following receipt of data, a USAF computer system was created to define this link, but precise definition of total conceptions, live births and nonlive births must await verification by receipt of birth certificates and medical records. This processing is presently ongoing and will be finalized in future reports. Of the 7399 conceptions analyzed in this report 3293 were reported by Ranch Handers or their spouses and 4106 were reported by the total comparison group or their spouses. Comparison conception included 2669 in the subset of originally selected comparison individuals and 1437 in the group of shifted and replacement comparisons.

2. Fertility/Infertility

Data on the number of conceptions, number of marriages, duration of marital and nonmarital relationships, and the number of couples with the desired number of children were gathered during the in-home questionnaire. Three reproductive indices were derived from these data; the Infertility Index (number of childless marriages per total number of marriages), the Married Fertility Index (number of conceptions per years of marriage) and the Total Fertility Index (number of conceptions per years together). The Total Fertility Index includes time spent in nonmarital relationships. The data on fertility/infertility outcomes are presented in Table XI-1.

Table XI-1

FERTILITY/INFERTILITY OUTCOMES
FOR QUESTIONNAIRE COMPLIANT INDIVIDUALS

Variable	Group RH	Group OC	Group AC	P value; RH versus Originals	P value; RH versus All
Number of participants	1174	956	1531	-	-
Number of Marriages	1456	1167	1860	-	-
Number of conceptions	3292	2668	4106	-	-
Number of participants with conceptions	1043	856	1359	-	-
Mean number of conceptions per participant	2.80	2.79	2.68	-	-
Mean number of marriages	1.24	1.22	1.21	-	-
Number of childless marriages	385	283	448	-	-
Infertility index	0.264	0.243	0.241	0.32	0.23
Number of couples with children, having the desired number of children	708	560	891	0.67	0.73
Married fertility index	0.165	0.155	0.158	>0.25	>0.25
Total fertility index	0.163	0.154	0.157	>0.25	>0.25

RH = Ranch Hand
OC = Original Comparisons
AC = All Comparisons

Although the crude numbers of conceptions and childless marriages differ between the Ranch Hand and comparison groups, the mean number of conceptions per participant and the proportion of marriages without children are not different. The percentages of couples with children who had the desired number of children, are not significantly different.

Two hundred eighty-three of the 1045 Ranch Handers (27.1%) and 211 of the 733 originally selected comparisons (27.3%) attending the physical examination had vasectomies (P = 0.92). Seven hundred fifty-eight of the Ranch Handers (72.5%) and 561 of the comparisons (76.5%) submitted semen specimens. Of those participants willing and able to provide semen specimens, 186 Ranch

Handers and 140 comparisons had vasectomies and/or orchiectomies (N = 6) and were therefore excluded from the statistical analysis of sperm counts. Six of these participants with a history of vasectomy were found to have sperm in their specimen and they were informed of these findings.

The semen specimens from the remaining 993 participants were analyzed by general linear model techniques, using continuous variables of sperm count and the percentage of each participant's sperm which had abnormal morphology. The means, standard deviations and median values for the sperm counts and percent of sperm with abnormal morphology are displayed in Table XI-2. These analyses were adjusted for age and exposure to industrial chemicals, and revealed no significant group differences in sperm counts (adjusted P = 0.77), or in the percentage of abnormal sperm morphology (adjusted P = 0.71). Twenty-seven Ranch Handers and 19 comparisons had abnormal sperm morphology out of 560 and 409 analyzed specimens, respectively. Unprotected exposure to industrial chemicals (ever, never) had no significant effect in these analyses. However, age had a significant effect on sperm count (P = 0.0001), with sperm count increasing with age. The relevance of this observation is unclear since the counts may be biased somewhat by the differential compliance observed with increasing age. Compliance differed significantly with age (P < 0.001) but not by group (P = 0.78). This in sperm count increase was the same in both the Ranch Hand and comparison groups, with a slope of 1.69 in the Ranch Hand/original analysis, and 1.85 in the Ranch Hand/all analysis. These slopes were significantly different from zero (P = 0.0001). There was no significant association between age and abnormal sperm morphology (adjusted P = 0.57). The distribution of sperm counts in the two groups is presented in Figure XI-2, and the distribution of abnormal sperm morphology percentage is displayed in Figure XI-3. The patterns of compliance to semen specimen collection is shown in Figure XI-4.

Table XI-2

DESCRIPTIVE STATISTICS OF SPERM VARIABLES BY GROUP

	Mean	Standard Deviation	Median	P value
Count (in million/ml)				
Original Comparisons	111.864	108.833	80	0.77
Ranch Hand	111.469	102.782	86	
All Comparisons	111.025	108.475	78	0.99
Percent Abnormal Sperm				
Original Comparisons	9.614	5.182	9	0.71
Ranch Hand	9.705	5.525	9	
All Comparisons	9.643	5.946	8	0.79

Figure XI-2

DISTRIBUTION OF SPERM COUNTS BY GROUP

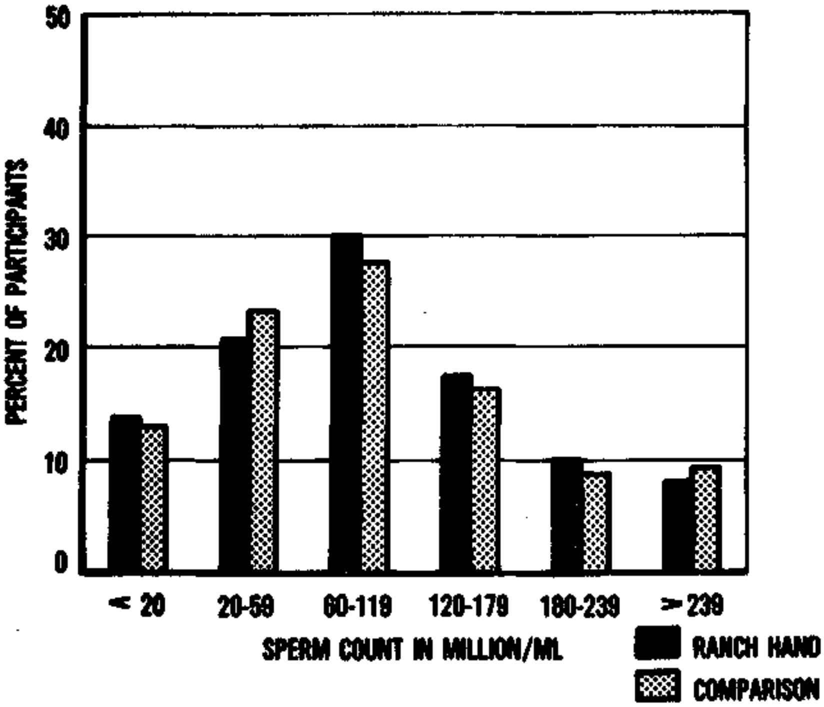


Figure XI-3

DISTRIBUTION OF ABNORMAL SPERM BY GROUP

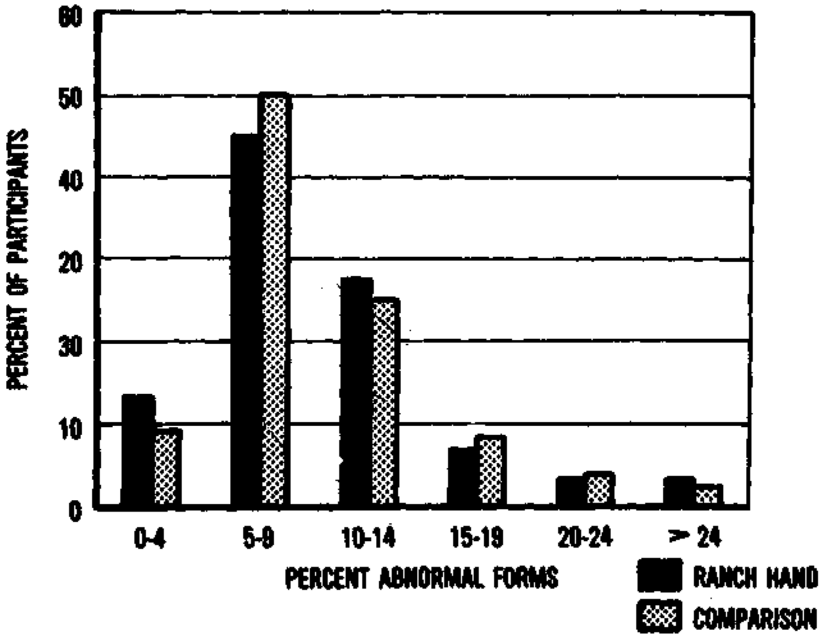
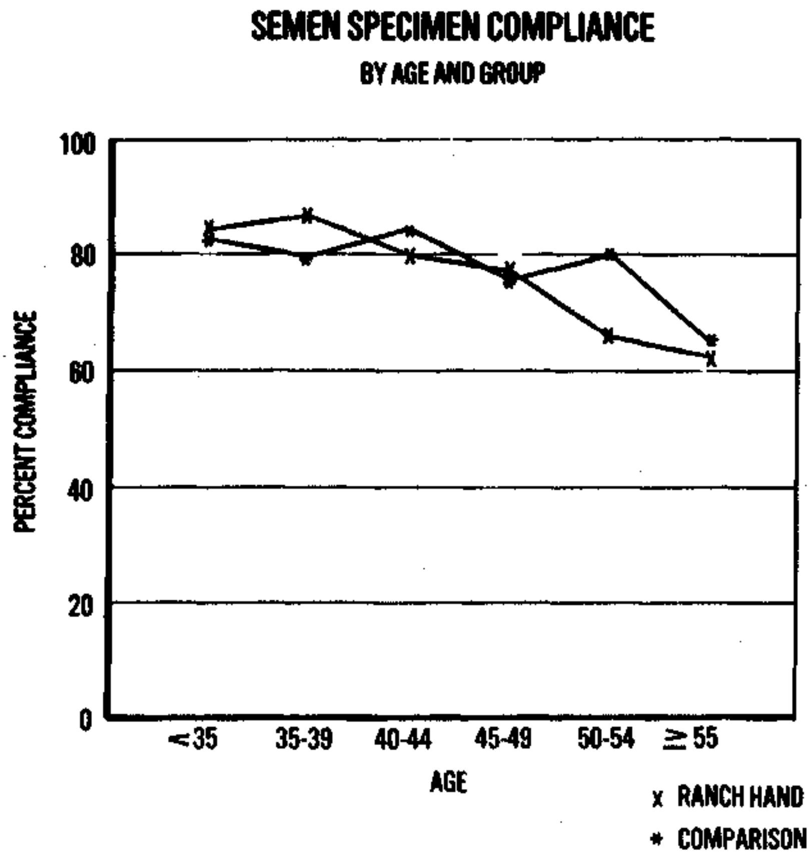


Figure XI-4



3. Conception Outcomes

In the evaluation of the outcomes of pregnancies fathered by study participants, analyses were conducted on all reported pregnancies in which the date of conception was known, and repeated on a subset of those in which information on maternal age, maternal smoking, and drinking habits was available from spouse questionnaires (complete data subset). There were an additional 95 conceptions in which data were too incomplete for analysis, and thus were deleted from the data base.

There is no difference in the pattern of missing data between the two groups, as shown in Table XI-3.

Table XI-3

COMPLETENESS OF CONCEPTION INFORMATION

Group	Complete Data	Partial Data	Incomplete Data	P Values
Original Comparisons	2278 (85.4%)	348 (13.0%)	42 (1.6%)	0.59
Ranch Hand	2781 (84.5%)	459 (13.9%)	53 (1.6%)	
All Comparisons	3435 (83.7%)	599 (14.6%)	72 (1.8%)	0.64

The occurrence of miscarriage was determined for each conception in which a date was reported. Similarly, outcomes of induced abortion, stillbirth and live birth were also determined. Adjustments for maternal factors of age (< 35, ≥ 35), smoking (yes, no) and alcohol use (yes, no) and paternal age (< 35, ≥ 35) could not be performed on these pregnancies with partial data, and no analysis was possible on those with incomplete data. In the covariate adjusted analyses, the primary statistical relationship of interest is the complex relationship between group outcome and time. Use of the pre-SEA conception experiences allows the Ranch Hand pre-SEA conceptions to serve as a standard for comparison with post-SEA conceptions. This is of special importance since 63.2% of the Ranch Hand and 63.6% of the comparison conceptions were pre-SEA events. Table XI-4 presents the data and the results of the analysis of these outcomes. Similar analyses using data from the entire comparison group are presented in Appendix X. The results of these additional analyses were essentially the same as those in Table XI-4.

Table XI-4

ANALYSES OF CONCEPTION OUTCOMES, UNADJUSTED FOR MATERNAL COVARIABLES (COMPLETE AND PARTIAL DATA SUBSETS); RANCH HANDERS VERSUS ORIGINAL COMPARISON

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Miscarriage						
Ranch Hand	295	(14.4)	1754	190	(15.9)	1001
Comparison (O)	205	(12.3)	1467	130	(13.6)	825
	P = 0.06			P = 0.13		
Stillbirth						
Ranch Hand	13	(0.6)	2036	16	(1.3)	1175
Comparison (O)	13	(0.8)	1659	8	(0.8)	947
	P = 0.60			P = 0.27		
Induced Abortion						
Ranch Hand	13	(0.6)	2036	62	(5.2)	1129
Comparison (O)	14	(0.8)	1658	65	(6.8)	890
	P = 0.47			P = 0.12		
Live Birth						
Ranch Hand	1723	(84.1)	326	917	(77.0)	274
Comparison (O)	1435	(85.8)	237	744	(77.9)	211
	P = 0.15			P = 0.62		

These data demonstrate a borderline significant group difference in miscarriage ($P = 0.06$) prior to Southeast Asia duty and a suggestion of a difference ($P = 0.13$) post-SEA. However, inferences based on these analyses, unadjusted for key factors affecting pregnancy outcome, are of questionable value. Therefore, those conceptions in which full covariate information was known, were analyzed in greater detail.

The data reflecting outcomes for both pre- and post-SEA conceptions are shown in Table XI-5, and the results of the adjusted analyses are displayed in Table XI-6.

Table XI-5

CONCEPTION OUTCOMES (COMPLETE DATA SUBSET)
BY GROUP MEMBERSHIP AND TIME;
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Miscarriage						
Ranch Hand	239	(13.7)	1505	156	(15.0)	883
Comparison	172	(11.9)	1276	104	(12.5)	726
	P = 0.13			P = 0.12		
Stillbirth						
Ranch Hand	9	(0.5)	1735	12	(1.2)	1027
Comparison	8	(0.6)	1440	8	(1.0)	822
	P = 0.89			P = 0.69		
Induced Abortion						
Ranch Hand	8	(0.5)	1736	37	(3.6)	1002
Comparison	7	(0.5)	1441	33	(4.0)	797
	P = 0.92			P = 0.61		
Live Birth						
Ranch Hand	1487	(85.3)	257	833	(80.2)	206
Comparison	1258	(86.9)	190	682	(82.2)	148
	P = 0.19			P = 0.27		

Table XI-6

RESULTS OF THE ANALYSIS OF CONCEPTION OUTCOMES;
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

Relationship	P value
Miscarriage by Group by Pre/Post-SEA	0.76
Stillbirth by Group by Pre/Post-SEA	1.00
Induced Abortion by Group by Pre/Post-SEA	0.89
Live Birth by Group by Pre/Post-SEA	0.94

Although a group difference of 15% versus 12.5% in post-SEA miscarriage is observed ($P = 0.12$), both groups had similar post-SEA conception outcomes relative to their own pre-SEA baseline experiences ($P = 0.76$). Ranch Hand miscarriages increased from 13.7% pre-SEA to 15.0% post-SEA while comparison miscarriages increased from 11.9% to 12.5%. Thus, while more Ranch Hand conceptions resulted in miscarriages than the comparisons, they started from a higher level before their herbicide exposures occurred, and in the overall analyses, there was no significant difference. These rates of miscarriage are comparable to estimates of 10-20% for the general US population (Last, 1980). The rate of stillbirths in the US population is 0.98%, again comparable to the observed rates in this study. Similar analyses were conducted using data from all comparison individuals, and the results of these procedures were similar to those presented in Table XI-6. The data and analytic results of these additional analyses are shown in Appendix X.

The effect of increasing maternal age was evident in all of these measures, with highly significant increases in miscarriage and induced abortion and decreases in live births associated with increasing age ($P \leq 0.01$). The increase in induced abortions in both groups is unexplained, but is most likely the result of the altered legal status of induced abortion and its increased social acceptance.

Exposure index analyses were performed in each of the three occupational categories (Officers; Enlisted, Flying; and Enlisted, Ground). The degree of exposure in each of these categories was stratified as low, medium or high (see Chapter VIII). Since the stratification by occupational category and exposure level and patterns of missing covariate data resulted in smaller groups, analyses had to be conducted using each covariate separately. A single analysis using all covariates would have resulted in unacceptably small cell sizes for meaningful analysis. The number of conception outcomes by occupational category available for each covariate analysis are presented in Table XI-7, and results of each covariate analysis are shown in Table XI-8.

Table XI-7

NUMBER AND RESULT OF CONCEPTION OUTCOMES FOR EACH COVARIATE ANALYSIS BY OCCUPATIONAL CATEGORY

		Category					
		Officers		Enlisted Flying		Enlisted Ground	
Parameter	Covariable	Yes	No	Yes	No	Yes	No
Miscarriage	Maternal Smoking	34	225	19	100	102	542
	Maternal Alcohol	34	225	19	100	102	542
	Maternal Age	44	241	22	119	122	608
	Paternal Age	44	250	22	119	122	617
Stillbirth	Maternal Smoking	2	257	2	117	7	637
	Maternal Alcohol	2	257	2	117	7	637
	Maternal Age	3	282	2	139	8	722
	Paternal Age	4	290	2	139	9	730
Induced Abortion	Maternal Smoking	17	242	6	113	14	630
	Maternal Alcohol	17	242	6	113	14	630
	Maternal Age	18	267	9	132	23	707
	Paternal Age	24	270	9	132	29	710
Live Birth	Maternal Smoking	205	54	92	27	521	123
	Maternal Alcohol	205	54	92	27	521	123
	Maternal Age	219	66	108	33	576	154
	Paternal Age	219	75	108	33	576	163

Table XI-8

RESULTS OF THE CONCEPTION/EXPOSURE INDEX ANALYSES

		Outcome/Exposure P Value, Adjusted for:			
		Maternal			Paternal
Parameter	Occupational Category	Smoking	Alcohol	Age	Age
Miscarriage	Officers	0.04	0.04	0.07	0.06
	Enlisted, Flying	0.30	0.26	0.19*	0.20
	Enlisted, Ground	0.54	0.50	0.62	0.51
Stillbirth	Officers	-	-	-	-
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	-	-	-	-
Induced Abortion	Officers	0.12	0.12	0.04*	<0.01*
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	0.25	0.25	0.48	0.43*
Live Birth	Officers	0.27	0.24	0.57*	0.59*
	Enlisted, Flying	0.60	0.55*	0.37*	0.45
	Enlisted, Ground	0.24	0.23	0.29	0.43

* Three-way covariate interaction is present.
\- Data too sparse for valid statistical analysis

The only statistically significant findings observed are for miscarriage and for induced abortion among officers. Consistent patterns of increasing adverse outcomes of pregnancy with increasing herbicide exposure are not evident for other outcomes. In all four covariable analyses in the officer group, there was a significant association between miscarriage and exposure level (low, medium and high).

4. Live Birth Outcomes

Those conceptions resulting in a live birth were further analyzed to determine the frequency of adverse events in those infants and children. As in the assessment of conceptions, unadjusted analyses were conducted on all reported live births in which a date of conception was known or could be estimated from the known date of birth. Analyses were repeated on those live births for which information on maternal age, maternal smoking, and maternal use of alcohol were available. Table XI-9 presents the distribution of live births within the subsets with complete and partial data. The difference in the proportion of the groups with only partial data are not statistically significant. Those births with inadequate data are omitted.

Table XI-9

COMPLETENESS OF LIVE BIRTH DATA

	Complete Data	Partial Data	Total	P Values
Original Comparisons	1940 (89.0%)	239 (11.0%)	2179	0.21
Ranch Hand	2320 (87.8%)	320 (12.2%)	2640	
				0.43
All Comparisons	2922 (87.2%)	429 (12.8%)	3351	

Based on in-home questionnaire responses and respondent definitions of gestational age, there were no differences in the occurrence of prematurity, and postmaturity in the Ranch Hand and comparisons groups (P=0.85). Further analyses of the incidence of prematurity based on objective criteria of birth weight will be conducted after birth certificate verification.

Information concerning learning disabilities, physical handicaps, birth defects and the occurrence of neonatal and infant death was collected for each live birth. The information was obtained as a "yes" response primarily from the spouse questionnaire. Study subject responses were used when spouse data were unavailable. Data collection questions included: "Did (child) have any birth defects?"; "Does/Did (child) have a diagnosed learning disability?"; and "Does/Did (child) have any physical, mental, or motor impairments?" Yes responses to all 3 questions had been coded by the USAF from the ICD-9-CM based on the mother's or father's statement concerning the kind of birth defect, learning disability or physical, mental or motor impairment. For each defect reported for each child, the interviewer had the opportunity to document 3 statements within the question regarding the kind of birth or developmental problem. Therefore, each yes response had in some cases 3 ICD-9-CM codes. A computer program was written to select defined birth defects, learning disabilities and physical, mental and motor impairments. For the child with multiple reported birth defects, he/she was counted only once for analysis. For children with multiple reported birth defects the most serious condition was analyzed. This report contains data on children with reported defects and not all reported defects; analyses of total reported defects will occur in a future report. A thorough review of the birth defect codes including key punch and code verification was accomplished prior to analysis of the merged data file. This review was not accomplished for reported learning disabilities or physical, mental and motor impairments, neonatal or infant death. The comprehensive definition of those reported defects within the definition for this report are presented in Appendix V. Reported birth defects not within the acceptable definition are presented in Appendix XIX.

Counts of the total-reported and within-definition birth defects are presented in Table XI-10. Fifty-nine percent of the Ranch Hand and 64% of the total comparison reported defects were within the acceptable defined range of birth defect.

Table XI-10

COUNT AND PERCENT OF TOTAL REPORTED
WITHIN-DEFINITION BIRTH DEFECTS

	Total Reported	Within Definition	P Values
Original Comparison	218	137 (63%)	0.37
Ranch Hand	292	172 (59%)	
All Comparisons	334	212 (64%)	0.24

The 5-6% difference in the perception of conditions which constitute a birth defect is not statistically significant. However, differential reporting of birth defects is of concern because media attention to hypothesized effects from exposure to the herbicide may affect parental reporting. In addition literature suggests the possibility that parents could perceive post-SEA births as "vulnerable" children (McCormick, 1982). Because of the above factors, all reported defects within range were categorized as severe, moderate, and limited (those of minor medical consequence) birth defects. This approach is based on a recent study (Christianson, 1981) which demonstrated that the incidence of reported congenital anomalies increased as children aged. Living children with reported defect average 23 years of age at the present time, with an age range of 2 through 39 years, and therefore, many years of parental observation have elapsed. The definition used for the collapsing of data into this system are as follows:

Severe: Conditions which are life threatening or produce severe handicaps (e.g., physical, mental, motor).

Moderate: Conditions which are not life threatening and handicaps which with medical care will not interfere with the individual's overall health or socio-economic progress.

Limited: All conditions which without medical care would not interfere with the individual's health or socio-economic progress. Those reported birth defects without type of defect data were included in the limited category.

Responses to birth defects which were unclear, incomplete or could be classified into more than one category were classified in the highest category applicable to the condition.

Table XI-11 summarizes the reported birth defects categorized by level of severity system.

Table XI-11

SUMMARY OF CHILDREN REPORTED WITH BIRTH DEFECTS BY LEVEL OF SEVERITY (SEVERE, MODERATE, LIMITED) RANCH HAND AND COMPARISON, PRE AND POST SEA TOUR

Nature of Reported Defect	Ranch Hand Counts	Ranch Hand %	Original Comparisons Counts	Original Comparisons %	Total Comparisons Counts	Total Comparisons %
PRE-SEA						
Severe	51	56.5	50	57	62	51
Moderate	32	35.5	27	31	40	33
Limited	7	8	10	12	20	16
TOTAL	90	100	87	100	122	100
POST-SEA						
Severe	32	40	18	37.5	34	40
Moderate	22	27.5	20	41.5	34	40
Limited	26	32.5	10	21	18	20
TOTAL	80	100	48	100	86	100
TOTAL (PRE AND POST-SEA)						
Severe	83	49	68	50	96	46
Moderate	54	32	47	35	74	36
Limited	33	19	20	15	38	18
TOTAL	170	100	135	100	208	100

This table shows that overall, 19% of the Ranch Hand, 15% of the original and 18% of the total comparison group reported birth defects were classified as "limited." Ranch Handers reported 8% limited pre-SEA and 32.5% post-SEA. Original comparisons reported 12% pre-SEA and 21% post-SEA and total comparisons reported 16% and 20%, respectively. These observations will be analyzed more fully in subsequent reports.

Table XI-12 presents the analysis of the live birth outcomes for the partial and complete data subsets unadjusted for maternal factors of smoking, age and alcohol use.

Table XI-12

ANALYSES OF LIVE BIRTH OUTCOMES, UNADJUSTED FOR MATERNAL COVARIABLES (COMPLETE AND PARTIAL DATA SUBSETS); RANCH HANDERS VERSUS ORIGINAL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Learning Disability						
Ranch Hand	61	(3.5)	1662	77	(8.4)	840
Comparison	62	(4.3)	1373	51	(6.9)	693
		P = 0.26			P = 0.24	
Physical Handicaps						
Ranch Hand	144	(8.3)	1579	132	(14.4)	785
Comparison	112	(7.4)	1323	85	(11.4)	659
		P = 0.57			P = 0.07	
Infant Death						
Ranch Hand	8	(0.5)	1715	4	(0.4)	913
Comparison	3	(0.2)	1432	3	(0.4)	741
		P = 0.23			P = 0.92	
Birth Defects						
Ranch Hand	90	(5.2)	1633	80	(8.7)	837
Comparison	87	(6.1)	1348	48	(6.5)	696
		P = 0.31			P = 0.08	
Neonatal Death						
Ranch Hand	25	(1.5)	1698	14	(1.5)	903
Comparison	17	(1.2)	1418	3	(0.4)	741
		P = 0.51			P = 0.02	

Live birth outcomes were not statistically different in the 2 groups prior to the participants tour of military duty in SEA. However, 3 of the 5 measures of outcomes after SEA duty demonstrated borderline or statistically significant differences between the Ranch Hand and comparison groups. The significant findings in neonatal deaths (P = 0.02), and the borderline significant finding for birth defects (P = 0.08) and physical handicaps (P = 0.07) were not adjusted for the effects of key covariables. Therefore, the data from those live births with full covariate information (complete data subset) concerning the maternal covariables were analyzed. Table XI-13 displays the pre-SEA and post-SEA data from this subset of births.

Table XI-13

LIVE BIRTH OUTCOMES (COMPLETE DATA SUBSET);
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

Parameter	Group	Pre-SEA			Post-SEA		
		Yes	(%)	No	Yes	(%)	No
Learning	RH	57	(3.8)	1430	75	(9.0)	758
Disability	Comp	57	(4.5)	1201	47	(6.9)	635
Physical	RH	134	(9.0)	1353	126	(15.1)	707
Handicap	Comp	103	(8.2)	1155	77	(11.3)	605
Infant	RH	7	(0.5)	1480	3	(0.4)	830
Death	Comp	2	(0.2)	1256	1	(0.1)	681
Birth	RH	78	(5.2)	1409	76	(9.1)	757
Defects*	Comp	80	(6.4)	1178	44	(6.5)	638
Neonatal	RH	20	(1.3)	1467	14	(1.7)	819
Death	Comp	17	(1.4)	1241	3	(0.4)	679

*Analysis includes 2 Ranch Hand birth defects which were double counted.

Log-linear analyses, simultaneously considering all covariates (maternal age, maternal smoking, and maternal alcohol use, and paternal age) were accomplished. Table XI-14 confirmed the differences in birth defects initially seen in the unadjusted analyses of post-SEA live births. This finding was statistically significant (P = 0.04) after adjusted analysis. Suggestive associations were noted in learning disabilities (P = 0.19) and in neonatal deaths (P = 0.20). Incidence rates of neonatal death and infant death in the general US population are estimated to be 0.99% and 1.4%, respectively (Last, 1980). The incidence rate of major birth defects in the general population is estimated to be 3-5%, but varies, depending upon the criteria used to define the "defects."

Table XI-14

RESULTS OF THE ANALYSIS OF LIVE BIRTH OUTCOMES;
RANCH HANDERS VERSUS ORIGINAL COMPARISONS

Relationship	P Value
Learning Disability by Group by Pre/Post SEA	0.19
Physical Handicap by Group by Pre/Post SEA	0.45
Infant Death by Group by Pre/Post SEA	0.81
Birth Defects by Group by Pre/Post SEA	0.04
Neonatal Death by Group by Pre/Post SEA	0.20

The distribution of reported post-SEA birth defects is presented in Table XI-15. This table clarifies the reported birth anomalies by level of medical consequence. Twelve congenital anomalies of the skin (ICD code 757) are present in the Ranch Hand data. This category of skin anomalies is quite broad, and includes simple birth marks, pigmentary changes, and more serious conditions. Reanalysis of the data concerning birth defects among live births in which full covariate data were available was accomplished with skin anomalies deleted. The birth anomalies included in the ICD category 757 are generally of minor medical consequences and their removal from analysis can be expected to provide a clearer understanding of group differences in birth defects of major health significance. This analysis revealed no significant group difference between Ranch Hand and comparison group live births for the remaining nonskin birth anomalies ($P = 0.14$). However, this weak association is still of interest. All reported birth defects are presently being validated by medical record reviews. Significant associations were noted ($P < 0.05$) between maternal smoking during pregnancy and learning disabilities, physical handicaps, infant deaths and birth defects. Maternal alcohol use during pregnancy was also associated with physical handicaps ($P < 0.001$). Future analyses of the birth defect data will also make use of the severity level classification. Live birth analyses using data from all of the comparisons were also conducted, and are contained in Appendix X. These analyses identified significant group differences in physical handicaps, birth defects and neonatal deaths. However, the influences of increased sample size and potential replacement group bias (differential reporting) have not been taken into consideration in these analyses.

Table XI-15

COUNTS OF ANALYZED POST-RVN BIRTH DEFECTS REPORTED BY RANCH HANDERS AND ORIGINAL COMPARISONS BY ICD CODE, LEVEL OF SEVERITY, AND AS STATED BY PARENT

ICD-9-CM Codes	Ranch Hand Level of Severity S	M	L	Nomenclature Reported by Spouse/Study Subject	Original Comparisons Level of Severity S	M	L
228	1			Blood tumor on nose			
				Hemagioma on left portion of head and face		1	
5240				Micrognathia	1*		
5531				Umbilical hernia		1	
741	1*			Spina bifida			
	1*			Open spine (severe case of Spina bifida)			
742	1*			Spinal cord and brain not connected			
	1*			Brain damage			
743			1	Slightly, eye coordination			
744	1			Deaf in left ear (nerve under-developed)			
				Malformed ear		1	
		2		Bump on ear			
		1		Missing small part of right earlobe			
745	1			Septal defects	2		
	1*			Double outlet right ventricle			
				Heart murmur	1		
	1			Foramen ovale was not totally closed			
746	1			A congenital heart			
	1			Heart valve			
	1			Heart SV node, two nodes in heart			
				Heart condition		1	
	1			Blue baby	1		
747	3			Patent ductus			
			1	Varicose vein in right groin			
748	2*			Underdeveloped lungs, Premature			
			1	Spot on lung			

Table XI-15 (Cont)

COUNTS OF ANALYZED POST-RVN BIRTH DEFECTS REPORTED BY RANCH HANDERS AND ORIGINAL COMPARISONS BY ICD CODE, LEVEL OF SEVERITY, AND AS STATED BY PARENT

ICD-9-CM Codes	Ranch Hand Level of Severity S	Ranch Hand Level of Severity M	Ranch Hand Level of Severity L	Nomenclature Reported by Spouse/Study Subject	Original Comparisons Level of Severity S	Original Comparisons Level of Severity M	Original Comparisons Level of Severity L
749	2			Cleft lip	2		
	1			Cleft palate			
750				Pyloric stenosis	1		
				Skin growing across his esophagus	1		
		1		Large bubble or abscess on throat			
	1			TE fistula			
			4	Tongue tied			
751	1*			Couldn't eat her food			
752				Undescended testicle		3	
		1		Hypospadia			
		1		Opening for urinating lower than normal			
				Vagina fused, had operation		1	
753	1			Defective kidney			
	1			Malformation of right kidney			
		1		Infantile polycystic kidney disease			
754				Talipes	2		
				Club foot	2		
				Dislocated hips		3	
				Leg bowed in at birth required cast and then braces		1	
		1		Chest cavity deformity			
				Ankle bones deformed		2	
			5	Foot turned in			
				Toes turned in			1
755				Left hand had no fingers, has thumb	1		
				Crooked femur bone	1		
	1			Possible hip or feet or both developed later			
				Deformed feet		2	
		1		Two toes joined together			
				Hip and foot defect, wore a brace		1	
		1		Extra finger and toe			

Table XI-15 (Cont)

COUNTS OF ANALYZED POST-RVN BIRTH DEFECTS REPORTED BY RANCH HANDERS AND ORIGINAL COMPARISONS BY ICD CODE, LEVEL OF SEVERITY, AND AS STATED BY PARENT

ICD-9-CM Codes	Ranch Hand Level of Severity S	M	L	Nomenclature Reported by Spouse/Study Subject	Original Comparisons Level of Severity S	M	L
		1		Leg turned in, wore a cast for 3 months			
		1		Bones from knees to ankles grew inward			
			1	Webbed finger on hand			
				Delta phalanges of index fingers			1
			3	Crooked foot or legs			
			1	Leg problem, knees hurt as infant			
756	1			Unusually tiny head			
	1			Premature fusion of sagittal sutures			
				Skull slightly deformed		1	
		1		Bone deformity			
				Small neck muscles from being in breach position		1	
			1	Feet curved in at birth			
757				Ichthyosis	1		
		1		No finger or toe nails			
		2		Skin pigmentation			
			1	Skin discoloration			
			1	Yellow color, disappeared in a week			
			5	Birthmarks			1
			1	Two nipples on breast			
			1	Skin tags			1
758	2			Down's Syndrome	3		
TOTAL	30	18	26	= 74	19	19	6 = 44

*Child deceased.

Table XI-15 relates the ICD codes to the level of severity to the reported statement of the spouse or study participant. Of the 74 post-RVN Ranch Hand reported birth defects, 30 are of a severe and 18 of a moderate level of severity. Counts of reported birth defects pre-RVN and post-RNV by occupational category are presented in Table XI-16. Inspection of this table shows that the increase in reported birth defects post-RVN are predominately from personnel in the Ranch Hand and total comparison enlisted ground occupational category. However, these data have not yet been adjusted by the number of live births in each occupational category.

Table XI-16

COUNTS OF REPORTED BIRTH DEFECTS PRE- AND POST-SEA BY OCCUPATIONAL CATEGORY (OFFICER, ENLISTED-FLYING, ENLISTED-GROUND)

Occupational Category	Ranch Hand Pre-SEA Counts	Ranch Hand Post-SEA Counts	Original Comparisons Pre-SEA Counts	Original Comparisons Post-SEA Counts	Total Comparisons Pre-SEA Counts	Total Comparisons Post-SEA Counts
Officer	44	15	40	16	52	22
Enlisted - Flying	13	12	15	5	21	10
Enlisted - Ground	21	49	25	23	40	45
TOTAL	78	76	80	44	113	77

Exposure analyses were performed using the covariates of maternal age, maternal smoking, maternal alcohol use, and paternal age. Each covariable was analyzed separately. The number and result of live birth outcomes by occupational category available for each covariate analysis are presented in Table XI-17 and the results of each covariate analysis are shown in Table XI-18.

Table XI-17

NUMBER AND RESULT OF LIVE BIRTH OUTCOMES FOR EACH COVARIATE ANALYSIS BY OCCUPATIONAL CATEGORY

		Category					
		Officers		Enlisted Flying		Enlisted Ground	
Parameter	Covariable	Yes	No	Yes	No	Yes	No
Learning Disability	Maternal Smoking	15	190	8	84	52	469
	Maternal Alcohol	15	190	8	84	52	469
	Maternal Age	16	203	8	100	53	523
	Paternal Age	16	203	8	100	53	523
Physical Handicap	Maternal Smoking	26	179	12	80	81	440
	Maternal Alcohol	26	179	12	80	81	440
	Maternal Age	26	193	13	95	86	490
	Paternal Age	26	193	13	95	86	490
Infant Death	Maternal Smoking	1	204	1	91	2	519
	Maternal Alcohol	1	204	1	91	2	519
	Maternal Age	1	218	1	107	3	573
	Paternal Age	1	218	1	107	3	573
Birth Defects	Maternal Smoking	12	193	11	81	50	471
	Maternal Alcohol	12	193	11	81	50	471
	Maternal Age	12	207	12	96	53	523
	Paternal Age	12	207	12	96	53	523
Neonatal Death	Maternal Smoking	3	202	4	88	6	515
	Maternal Alcohol	3	202	4	88	6	515
	Maternal Age	3	216	4	104	6	570
	Paternal Age	3	216	4	104	6	570

Table XI-18

RESULTS OF THE LIVE BIRTH/EXPOSURE INDEX ANALYSES

		Outcome/Exposure P Value, Adjusted for:			
		Maternal			Paternal
Parameter	Occupational Category	Smoking	Alcohol	Age	Age
Learning Disability	Officers	0.47	0.46	0.31	0.34
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	0.92	0.94	0.89	0.85
Physical Handicap	Officers	0.07	0.07	0.06	0.05
	Enlisted, Flying	0.89	0.69	0.47	0.56
	Enlisted, Ground	0.78	0.79*	0.76*	0.79
Infant Death	Officers	-	-	-	-
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	-	-	-	-
Birth Defects	Officers	0.02	0.02	0.02	0.02
	Enlisted, Flying	0.03	0.06	0.03	0.03
	Enlisted, Ground	0.39	0.35	0.46	0.41
Neonatal Death	Officers	-	-	-	-
	Enlisted, Flying	-	-	-	-
	Enlisted, Ground	-	-	-	-

- Data too sparse for valid statistical analysis.
* Significant three-factor interaction is present.

These results demonstrate consistency across all covariates for each of the live birth outcomes; however, as noted in Table XI-18, the data are sparse in many instances, especially for officer and enlisted flying personnel. Birth defects are found to have a statistically significant association with herbicide exposure level in the officer and enlisted flying groups. However, there is not a consistent increase in defects with increasing exposure in the officer category. In the enlisted flying group the adverse outcome did increase consistently with increasing exposure. The pattern in the officer group demonstrated a two-fold rise in the medium level but the highest exposure group had the lowest proportion of children with defects (1.2%). Physical handicaps in children of officers demonstrated borderline significance.

5. Summary

A summary of the findings of the fertility and reproductive analyses are displayed in Table XI-19.

Table XI-19

SUMMARY OF FERTILITY AND REPRODUCTIVE ANALYSES

	P Values						
					Exposure Analyses by Occupational Group		
	Unadjusted		Adjusted			Enlisted	Enlisted
Parameter	O	A	O	A	Officers	Flying	Ground
Infertility	NS	NS					
Sperm Count			NS	NS			
Sperm Abnormality			NS	NS			
Conception Outcomes							
Miscarriage	0.13	0.15	NS	NS	0.04	0.19	NS
Stillbirth	NS	0.10	NS	NS			
Induced Abortion	0.12	NS	NS	NS	0.12		NS
Live Birth	NS	NS	NS	NS	NS	NS	NS
Live Birth Outcomes							
Prematurity	NS						
Learning Disability	NS	0.05	0.19	0.12	NS		NS
Physical Handicap	0.07	<0.01	NS	0.02	0.05	NS	NS
Infant Death	NS	NS	NS	NS			
Birth Defects	0.08	0.04	0.04	0.02	0.02	0.03	NS
Defects Excluding Skin Anomalies			0.14	0.07			
Neonatal Death	0.02	<0.01	0.20	0.03			

NS = Nonsignificant
O = Original Comparisons
A = All Comparisons

The analyses in this chapter did not reveal any significant differences in fertility/infertility and sperm counts between the Ranch Hand and either comparison group. Conception outcomes of miscarriage, stillbirth, induced abortion and live births also were not found to differ significantly. Analyses unadjusted for known risk factors of pre-SEA conception history, maternal age, maternal smoking, and maternal alcohol use, and paternal age revealed a suggestive association for increases in miscarriage after the father's SEA service in the Ranch Hand group. However, this association and a borderline increase in post-SEA induced abortion in the original comparison group were not evident after consideration of these other risk factors. Analyses of these conception outcomes with the herbicide exposure index also did not reveal any evidence of herbicide effects. A statistically significant association between increasing herbicide exposure and miscarriage was identified in the officer group but this effect was not observed in the other occupational categories. Borderline significance was noted in officers for stillbirth and induced abortion, but these findings did not increase in occurrence with increasing exposure.

Significant differences were reflected in the analyses of live birth outcomes. These differences were observed for birth defects after the analyses were adjusted for parental covariates. There appeared to be a clustering of birth anomalies of the skin in children of the Ranch Handers. There were no significant group differences for other birth defects, but a suggestive association remained ($P = 0.14$) after reanalysis with the skin anomalies excluded. Suggestive group differences between the Ranch Handers and original comparisons were also observed after adjusted analysis for learning disability and neonatal death. Exposure analysis identified several findings of statistical and borderline significance; however, the patterns were not consistent across occupational strata. Overall, birth defects demonstrated statistical significance in the adjusted intergroup analysis, and 2 of the 3 occupational group exposure analyses.

A larger number of live birth outcome differences were observed in analyses comparing the Ranch Handers to the total comparison group; however, it is unclear whether these differences are true group differences, or are due to changes in sample size or replacement bias (differential reporting). The value of these analyses in making inferences is therefore limited at this time.

The findings in this chapter do require further evaluation of the possible link between herbicide/dioxin exposure and birth defects. The analyses have relied heavily on unverified spouse reports, and the effect of differential reporting of conception and birth outcomes in pregnancies and in children who the parent might perceive as "special" or "vulnerable" has not been evaluated. This evaluation will be conducted using birth certificates and medical records so that an analysis of verified fertility/reproductive data can be included in the report of the first follow-up physical examination.

Chapter XII

NEUROLOGICAL ASSESSMENT

1. Introduction

Neurological abnormalities have long been recognized as acute toxic effects following the exposure of humans to phenoxy herbicides and dioxin (Goldstein, 1959; Wallis, 1970; Berkley, 1963; Boeri, 1978). Signs and symptoms, such as hyporeflexia, a decrease in nerve conduction velocity, general muscular weakness and decreased sensation in the extremities have been noted. One study documented demyelination as a result of 2,4-D exposure (Dudley, 1972). While these effects have only been demonstrated acutely following heavy exposures, complaints of peripheral neuropathy are prominent among Vietnam veterans who have participated in the Veterans Administration Agent Orange Registry Program. Twelve percent of the 110,000 patients in the Registry had complaints compatible with symptoms of peripheral neuropathy. The recognized acute neurotoxicity of these chemicals and the prevalence of neurological complaints among veterans were primary factors in the decision to place a major emphasis on the neurological evaluation of participants in this study.

During the administration of the questionnaire, each subject was asked to provide information on any major health conditions he may have experienced. All reported neurological conditions were coded using the ICD-9-CM and group analysis of the distribution of the conditions was performed. As revealed in Table XII-1, there were no statistically significant differences in reported neurological diseases between the Ranch Hand and comparison groups.

Table XII-1

DISTRIBUTION OF REPORTED NEUROLOGICAL DISEASES BY GROUP MEMBERSHIP

Disease Category	Original Comparisons	Ranch Hand	All Comparisons
Inflammatory Diseases	2	3	3
Hereditary and Degenerative Diseases	2	1	3
Peripheral Disorders	7	7	11
Disorders of the Eye	15	14	21
Disorders of the Ear and Mastoid	14	23	21
	P = 0.73		P = 0.69

There were 1045 Ranch Handers, and 773 originally selected comparisons included in the analyses in this chapter. Where analyses were accomplished using the total comparison group, the data from 1194 comparisons were used. Some variation in numbers did occur due to missing data. In the analyses of the data obtained from the neurological evaluation, only those participants with a negative serological test for syphilis were included since chronic neurological disease can result from inadequately treated syphilis (5 Ranch Handers and no comparisons were found to have positive serological tests for syphilis.) In addition, data from 15 individuals found to have edema of the extremities on physical examination (8 Ranch Handers and 7 comparisons) were deleted from the analyses of the peripheral sensory nerve evaluation and nerve conduction velocities since edema can interfere with these clinical evaluations. Several covariables were considered in the analysis. The use of alcohol (dichotomized to ever/never); years of unprotected exposure to industrial chemicals (yes, no), insecticides (yes, no), and degreasing chemicals (yes, no); and 2-hour postprandial glucose levels equal to or greater than 120 mg/dl were used as covariates.

2. Cranial Nerve Status

The functional integrity of all 12 cranial nerves was assessed during the neurological examination. The specific cranial nerves and the examination parameters used in their evaluation are listed in Table XII-2.

Table XII-2

CRANIAL NERVE EVALUATION

Cranial Nerve	Parameter
I Olfactory	Sense of smell
II Optic	Visual fields
III Oculomotor	Pupillary reaction to light Ocular movement
IV Trochlear	Ocular movement
V Trigeminal	Facial sensation Corneal reflex Clenching jaw
VI Abducens	Ocular movement
VII Facial	Smile Palpebral fissure
VIII Acoustic	Balance (Romberg Sign)
IX Glossopharyngeal	Gag reflex
X Vagus	Speech Tongue position
XI Spinal Accessory	Palate and uvula movement Neck movement
XII Hypoglossal	Neck range of motion

Analysis of the examination data revealed no statistically significant differences in cranial nerve function between the Ranch Hand and comparison groups. No significant three-way interactions between the examination parameters, group membership and the covariables of glucose and alcohol were noted. These results are summarized in Table XII-3. Data from the entire comparison group are also presented.

Table XII-3

ANALYSIS OF CRANIAL NERVE FUNCTION

Cranial Nerve	Parameter	Group	# Normal	# Abnormal	P Values; Ranch Hand Versus Original Comparisons	P Values; Ranch Hand Versus All Comparisons
I	Smell, left	RH	1025	19	0.67	0.68
		OC	759	12		
		AC	1172	19		
	Smell, right	RH	1027	17	0.73	0.70
		OC	760	11		
		AC	1174	17		
II	Visual fields, left	RH	1037	3	0.91*	0.87*
		OC	768	2		
		AC	1186	3		
	Visual fields, right	RH	1038	2	0.43*	0.51*
		OC	768	3		
		AC	1186	4		
III	Light reaction	RH	1031	8	0.52	0.43
		OC	763	4		
		AC	1180	6		
III-IV, VI	Ocular movement	RH	655	349	0.82	0.49
		OC	486	265		
		AC	746	423		
V	Sensation, left	RH	1035	7	0.68	0.26
		OC	769	4		
		AC	1190	4		
	Sensation, right	RH	1038	4	0.99*	0.58*
		OC	770	3		
		AC	1191	3		
	Corneal reflex	RH	1043	2	0.75*	0.49*
		OC	772	1		
		AC	1193	1		
	Jaw clench	RH	1042	1	-	-
		OC	773	0		
		AC	1194	0		

Table XII-3 (Cont'd)

ANALYSIS OF CRANIAL NERVE FUNCTION

Cranial Nerve	Parameter	Group	# Normal	# Abnormal	P Values; Ranch Hand versus Original Comparisons	P Values; Ranch Hand versus All Comparisons
VII	Smile	RH	1035	4	0.65*	0.85*
		OC	767	2		
		AC	1186	4		
	Palpebral fissure	RH	986	59	0.84	0.70
		OC	731	42		
		AC	1131	63		
VIII	Balance	RH	833	207	0.69	0.26
		OC	625	148		
		AC	813	228		
IX	Gag reflex	RH	1030	15	0.67	0.58
		OC	760	13		
		AC	1180	14		
X	Speech	RH	1041	3	-	0.26*
		OC	770	0		
		AC	1190	1		
	Tongue in mid-line	RH	879	4	0.63*	0.51*
		OC	662	2		
		AC	1085	3		
XI	Palate and uvula movement	RH	1042	3	0.48*	0.26*
		OC	771	1		
		AC	1192	1		
XI, XII	Neck range of motion	RH	1004	41	0.44	0.24
		OC	748	25		
		AC	1158	36		

*P values are of limited validity due to small cell sizes in these analyses
RH = Ranch Hand
OC = Originally selected comparison
AC = All comparisons
 - = Cells containing zeros; P values not valid

The 18 neurological parameters listed in Table XII-3 were again analyzed with regard to occupational group and exposure level. The exposure index, stratified into 3 occupational groupings and 3 levels of exposure, was applied to these cranial nerve data. These results are summarized in Table XII-4. Fully adequate cell sizes were obtained in only 13 instances. In these analyses, in which no individuals in either group had abnormalities, statistical testing for significance was invalid, and P values are not given.

Table XII-4

CRANIAL NERVE FUNCTION VERSUS EXPOSURE LEVEL WITH EACH OCCUPATIONAL CATEGORY

Cranial Nerve	Parameter	Occupational Category	P Value
I	Smell, left	O/F	0.79
		E/F	0.67
		E/G	0.16
	Smell, right	O/F	0.01
		E/F	0.84
		E/G	0.31
II	Visual fields, left	O/F	0.05
		E/F	0.40
		E/G	0.44
	Visual fields, right	O/F	0.06
		E/F	0.40
		E/G	0.11
III	Light reaction	O/F	0.32*
		E/F	-
		E/G	0.28
III, IV, VI	Ocular movement	O/F	0.21*
		E/F	0.33*
		E/G	0.47*
V	Sensation, left	O/F	0.32
		E/F	0.12
		E/G	0.72
	Sensation, right	O/F	0.64
		E/F	0.34
		E/G	0.35
	Corneal reflex	O/F	-
		E/F	-
		E/G	0.55

Table XII-4 (Cont'd)

CRANIAL NERVE FUNCTION VERSUS EXPOSURE LEVEL WITH EACH OCCUPATIONAL CATEGORY

Cranial Nerve	Parameter	Occupational Category	P Value
	Jaw clench	O/F	0.64
		E/F	-
		E/G	-
VII	Smile	O/F	0.64
		E/F	0.57
		E/G	-
	Palpebral fissure	O/F	0.97*
		E/F	0.14
		E/G	0.12*
VIII	Balance	O/F	0.89*
		E/F	0.25*
		E/G	0.44*
IX	Gag reflex	O/F	0.99
		E/F	0.84
		E/G	0.20
X	Speech	O/F	0.38
		E/F	0.34
		E/G	0.11
	Tongue in midline	O/F	0.07*
		E/F	0.30*
		E/G	0.40*
XI	Palate and uvula movement	O/F	0.64
		E/F	-
		E/G	0.43
XI, XII	Neck range of motion	O/F	0.67*
		E/F	0.78
		E/G	0.46

O/F = Officer, flying E/F = Enlisted, flying E/G = Enlisted, ground
* = Cell sizes of 5 or less
\- = Cells containing zeros; P values not valid

3. Peripheral Nerve Status

The variables used in the assessment of peripheral nerve function were analyzed with the covariates of 2-hour postprandial glucose in excess of 120 mg%, history of alcohol use and unprotected exposure to industrial chemicals, insecticides and degreasing chemicals. There were statistical interactions between group membership (Ranch Hand and comparison) and insecticide exposure, and between insecticide exposure and the other covariables. Since these relationships have no impact on the primary question being addressed by this study, further statistical analyses of these interactions will not be undertaken at this time.

Analysis of the data pertaining to the peripheral nervous system is summarized in Table XII-5. Data from the entire comparison group are also presented. With the exception of a borderline association between group and Babinski reflex in the originals and a significant association in the entire comparison group, these analyses did not demonstrate statistically significant differences in neurological functions between the 2 groups. Matched pair analyses were performed on the Babinski reflex and the vibration sense data, using the Breslow matched logistic regression technique. A P value of 0.18 was found for the Babinski reflex and a nonsignificant P value of 0.47 was found for vibration sense. Significant interactions were, however, detected between postprandial glucose levels and several of the examination parameters. The association between abnormal glucose metabolism and peripheral neurological disease is well recognized (Scientific American, 1983) and its demonstration in this study reflects a degree of confidence in the quality of the neurological data collection process. These glucose by neurological disease associations are shown in Table XII-6. A positive history of alcohol use had borderline significance with pin prick (P = 0.07). In this analysis, a continuing effect of abnormal glucose is seen for vibration (P = 0.0005), patellar reflex (P = 0.03), Achilles reflex (P = 0.04), and light touch (P = 0.03). Alcohol use also had a borderline significant effect on pin prick (P = 0.07).

Table XII-5

ANALYSIS OF THE PERIPHERAL NERVOUS SYSTEM

Parameter	Group	# Normal	# Abnormal	P value; Ranch Hand versus Original Comparisons	P value; Ranch Hand versus All Comparisons
Pin prick	RH	934	97	0.94	0.76
	OC	691	73		
	AC	930	101		
Light touch	RH	958	73	0.78	0.67
	OC	707	57		
	AC	953	78		
Muscle Status (strength, bulk)	RH	1003	37	0.94	0.62
	OC	745	28		
	AC	1009	32		
Vibration	RH	954	78	0.38	0.30
	OC	698	67		
	AC	941	91		
Patellar Reflex	RH	1034	4	0.45	0.74
	OC	766	5		
	AC	1003	5		
Achilles Reflex	RH	995	39	0.62	0.62
	OC	746	26		
	AC	1005	35		
Biceps Reflex	RH	1030	8	0.53	1.00
	OC	767	4		
	AC	1032	8		
Babinski Reflex	RH	1024	9	0.10	0.03
	OC	770	2		
	AC	1039	2		

RH = Ranch Hand
OC = Original comparisons
AC = All comparisons

Table XII-6

POSTPRANDIAL GLUCOSE ABNORMALITIES VERSUS NEUROLOGICAL FINDINGS (RANCH HANDERS VERSUS ORIGINAL COMPARISONS)

Parameter	Examination Status	Glucose Status # Normal	# Abnormal	P Value
Light Touch	Normal	1406	259	0.03
	Abnormal	100	30	
Vibration	Normal	1402	250	0.0005
	Abnormal	106	39	
Patellar Reflex	Normal	1514	286	0.03
	Abnormal	5	4	
Achilles Reflex	Normal	1463	273	0.04
	Abnormal	48	17	
Pin prick	Normal	1369	256	0.23
	Abnormal	137	33	

The data from the Ranch Hand group were also analyzed against the exposure index. As shown in Table XII-7, there were no three-way interactions between occupational group, herbicide exposure and the neurological parameters evaluated. No statistically significant results were found in the analysis of exposure versus examination parameters. Borderline associations were noted for vibration in the enlisted flying group (P = 0.10) and for Babinski Reflex in the enlisted ground personnel (P = 0.09). The relevance of these findings, in the face of the other negative results, is unclear at this time. There were no distinct patterns of increasing abnormality with increasing exposure.

Table XII-7

PERIPHERAL NEUROPATHY BY EXPOSURE ANALYSES: SUMMARY OF P VALUES

	Occupational Group		
Parameter	Officer	Enlisted Flying	Enlisted Ground
Pin prick	0.78	0.99	0.47
Light Touch	0.40	0.83	0.81
Muscle Status	0.43	0.96	0.65
Vibration	0.94	0.10	0.96
Patellar Reflex	0.50	0.57	1.00
Achilles Reflex	0.35	0.53	0.60
Biceps Reflex	0.49	0.57	0.91
Babinski Reflex	0.57	0.53	0.09

4. Evaluation of Central Functioning

A brief evaluation of central nervous system coordination processes was accomplished, focusing on the presence of muscle tremor, finger-to-nose coordination, gait and balance as assessed by the modified Romberg Sign. These analyses are shown in Table XII-8. As in the analysis of the peripheral nerves, there were no significant interactions of these findings with chemical exposures or group membership; however, abnormal glucose metabolism was associated with abnormal balance (P = 0.0002) and the presence of tremor (P = 0.004). Alcohol also had a significant effect on the presence of tremor (P = 0.05) and a borderline effect on balance (P = 0.09). Breslow matched pair analysis of the tremor and coordination data revealed nonsignificant P values of 0.21 and 0.31 respectively.

Table XII-8

ANALYSIS OF CENTRAL FUNCTION

Parameter	Group	# Normal	# Abnormal	P values; Ranch Hand versus Original Comparisons	P values; Ranch Hand versus All Comparisons
Tremor	RH	985	55	0.19	0.36
	OC	742	31		
	AC	995	46		
Coordination	RH	992	48	0.44	0.59
	OC	743	30		
	AC	998	43		
Romberg Sign	RH	833	207	0.64	0.26
	OC	625	148		
	AC	813	228		
Gait	RH	1014	24	0.47	0.76
	OC	758	14		
	AC	1018	22		

RH = Ranch Hand
OC = Original comparisons
AC = All comparisons

Exposure analysis was performed on these parameters as well. Three-factor analysis of parameter by exposure level by occupational group again demonstrated no significant interactions. In these analyses, the herbicide exposure/coordination analysis yielded a suggestive association (P = 0.10). Again, there was a statistically significant association between an abnormal Romberg Sign and abnormal glucose metabolism (P = 0.002). Two-way analysis results are shown in Table XII-9.

Table XII-9

HERBICIDE EXPOSURE VERSUS ABNORMALITY OF CENTRAL FUNCTIONING
SUMMARY OF P VALUES

Parameter	P Values: Officers	Enlisted Flying	Enlisted Ground
Tremor	0.50	0.76	0.20
Coordination	0.07	0.16	0.63
Romberg Sign	0.89	0.25	0.44
Gait	0.54	0.38	0.11

5. Nerve Conduction Velocity

Nerve conduction was evaluated using a continuous measurement and analyzed using a general linear model technique for maximal statistical power. Velocities were measured from 2 locations in the ulnar nerve and from 1 position in the peroneal nerve. Covariables in these analyses included history of alcohol use (measured in drink-years), abnormalities in postprandial glucose levels (equal to or greater than 120 mg/dl), and unprotected exposure to industrial chemicals, insecticides and degreasing chemicals. No associations between the chemical exposures and conduction velocities were identified on covariate analysis; however, highly statistically significant associations were noted in both the Ranch Hand and comparison groups between alcohol use and glucose and conduction velocity. This association held for both measurements of the ulnar nerve ($P \leq 0.01$) with the velocity decreasing as the drink-years of alcohol increased. Glucose was found to be associated with conduction velocity in the peroneal nerve ($P = 0.002$) and both ulnar velocities ($P = 0.001$) with velocity decreasing as glucose level increased. These analyses did not demonstrate any significant intergroup differences in velocities in either nerve. The unadjusted and adjusted means and their respective P values are presented in Table XII-10. Similar analyses, using data from the entire comparison group, were performed with similar means and results.

Table XII-10

NERVE CONDUCTION VELOCITY (M/SEC) AND GROUP MEMBERSHIP

Nerve	Group (N)	Unadjusted Mean	P Value	Adjusted Mean	P Value
Ulnar	R (1035)	55.88	0.30	55.89	0.38
(above the elbow)	C (769)	56.15		56.12	
Ulnar	R (1042)	60.50	0.39	60.52	0.48
(below the elbow)	C (771)	60.73		60.71	
Peroneal	R (1041)	48.22	0.74	48.23	0.66
	C (769)	48.14		48.93	

Herbicide exposure analyses were performed using the covariates of occupational group serum glucose and history of alcohol use. These results are shown in Table XII-11.

Table XII-11

ADJUSTED MEAN NERVE CONDUCTION VELOCITY (M/SEC) AND EXPOSURE

Nerve	Exposure			
	Low	Med-High	High	P Value
Officers				
Ulnar (above elbow)	55.77	55.66	55.97	0.90
Ulnar (below elbow)	60.54	60.60	61.10	0.70
Peroneal	47.69	47.76	47.87	0.96
Enlisted Flying				
Ulnar (above elbow)	54.54	55.72	55.35	0.53
Ulnar (below elbow)	58.31	60.68	60.83	0.03
Peroneal	48.22	48.28	48.29	0.99
Enlisted Ground				
Ulnar (above elbow)	55.53	56.60	56.33	0.24
Ulnar (below elbow)	59.96	60.74	60.69	0.96
Peroneal	48.34	48.31	49.00	0.14

These exposure analyses have not demonstrated any consistent trends in conduction velocity and increasing exposure either within or between occupational categories. A single significant result (P = 0.03) was found in the distal ulnar nerve velocity in flying enlisted personnel, but there was no corresponding finding in the same nerve when measured over a larger distance above the elbow (P = 0.53). The borderline significance in the peroneal nerve velocity of ground enlisted personnel (P = 0.14) was not evident in the other occupational categories. Again, significant associations with glucose were noted, with P values falling between 0.06 and 0.005.

6. Summary

As summarized in Table XII-12, detailed analyses of the neurological examination data pertaining to the status of the cranial nerves, peripheral nerves and central functioning were performed.

Table XII-12

SUMMARY OF NEUROLOGICAL STATUS

Parameter	Analysis (P Values)			
		Exposure		
	Group	Off	Enl Fly	Enl Gnd
Cranial Nerves				
1	NS	0.01	NS	0.16
2	NS	0.05	NS	0.11
3	NS	NS	NS	NS
4	NS	NS	NS	NS
5	NS	NS	0.12	NS
6	NS	NS	NS	NS
7	NS	NS	0.14	0.12
8	NS	NS	NS	NS
9	NS	NS	NS	NS
10	NS	0.07	NS	0.11
11	NS	NS	NS	NS
12	NS	NS	NS	NS
Peripheral Nerves				
Pin Prick	NS	NS	NS	NS
Light Touch	NS	NS	NS	NS
Muscle Status	NS	NS	NS	NS
Vibration	NS	NS	0.10	NS
Patellar Reflex	NS	NS	NS	NS
Achilles Reflex	NS	NS	NS	NS
Biceps Reflex	NS	NS	NS	NS
Babinski Reflex	0.10	NS	NS	0.09
Control Function				
Tremor	0.19	NS	NS	NS
Coordination	NS	0.07	0.16	NS
Romberg	NS	NS	NS	NS
Gait	NS	NS	NS	0.11
Conduction Velocity				
Proximal Ulnar	NS	NS	NS	NS
Distal Ulnar	NS	NS	0.03	NS
Peroneal	NS	NS	NS	0.14

NS = Nonsignificant

With the exception of a borderline increase in the proportion of Ranch Handers with a positive Babinski reflex, there were no significant differences detected between the Ranch Hand and comparison groups with respect to neurological parameters. The Babinski reflex, however, did not show a significant relationship to past herbicide exposure. There were no consistent findings of increasing abnormality with increasing herbicide (dioxin) exposure. The relative risks and confidence intervals for the dependent variables analyzed in this chapter are included in Appendix XVIII. Thus, it appears at this time, that there are no neurological abnormalities in the Ranch Hand group that can be attributed to herbicide exposure in Vietnam.

The evaluation of neurological status among the participants in this study has demonstrated the ability to identify classical interactions between abnormal glucose metabolism and alcohol use and evidence of neurological abnormalities. These findings lend confidence to the validity of the negative findings of a chronic herbicide (dioxin) effect on the neurological system.

Chapter XIII

PSYCHOLOGICAL ASSESSMENT

Since 1961, psychological abnormalities have been ascribed to acute phenoxy herbicide exposure (Bauer, 1961). Subsequently, a wide range of psychological symptoms, including anxiety, depression, emotional instability, and asthenia have been reported following exposure (Monarca and di Vito, 1961; Kramer, 1974; Poland et al, 1971). Since many Vietnam veterans have expressed concern that their exposure to the defoliants during the war caused them to experience psychological and behavioral problems, the psychological functioning of the study participants was assessed in both the questionnaire and physical examination phases of the study. Overall, the responses of 1045 Ranch Handers, 1230 comparisons, and a subset of 773 originally selected comparisons were analyzed. Slight variations in these numbers occurred in some analyses due to missing data. Except where indicated, all analyses reported in this chapter used the data from the subset of originally selected comparisons. Each participant was asked whether he had ever experienced psychological illness. Additionally, six specific psychological dimensions were explored in detail in the questionnaire: depression, anxiety, erosion of skills, social isolation, fatigue, and aggressive or impulsive behavior. The questions used were selected from an extensive test battery, previously developed and validated (Robbins, 1982). More standardized measurements of psychological performance were obtained during the physical examination by the use of several standardized tests. The Cornell Index, the Minnesota Multiphasic Personality Inventory (MMPI), the Halstead-Reitan Battery and the Wechsler Adult Intelligence Scale (WAIS) were the primary testing instruments. Throughout much of this chapter, educational level (high school versus college) and rank (officer versus enlisted status) received special attention in all analyses. These variables are widely recognized as having major influences on psychological testing performance (Dalstrom, 1960) and their importance in the setting of the Air Force Health Study was very apparent. Dependent variables were stratified by education and rank, and in log-linear techniques, they were used as covariables. Table XIII-1 displays the education and rank distributions of the Ranch Hand and original comparison groups.

Table XIII-1

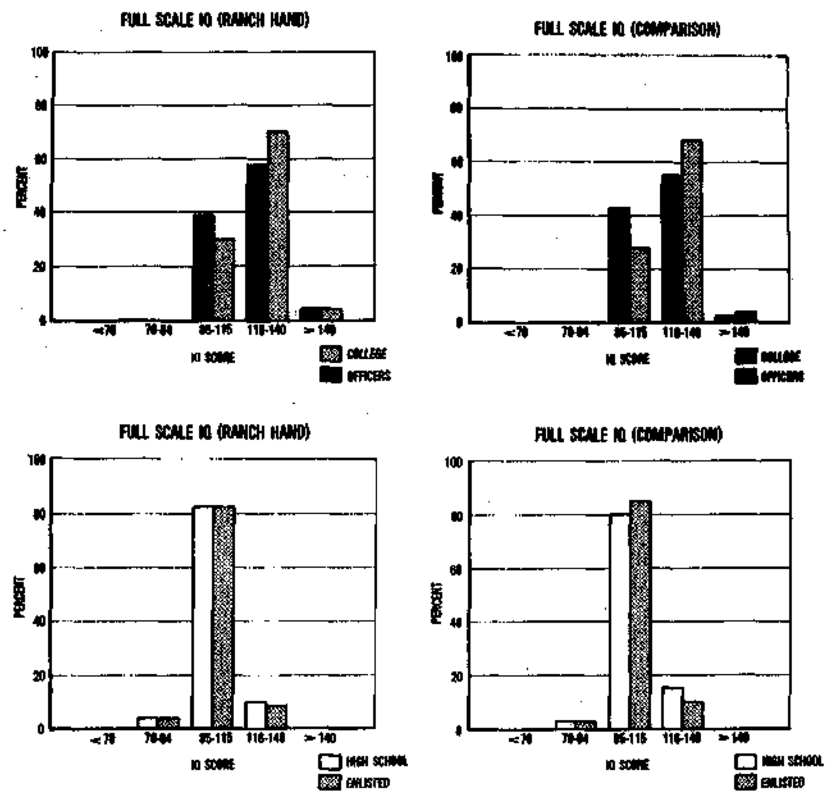
EDUCATION AND RANK DISTRIBUTION OF RANCH HAND AND ORIGINAL COMPARISON GROUPS

	Ranch Hand		Original Comparisons	
	High School	College	High School	College
Officers	54 (14.3%)	324 (85.7%)	53 (18.2%)	239 (81.8%)
Enlisted	521 (80.8%)	124 (19.2%)	377 (79.4%)	98 (20.6%)

Regardless of statistical technique or procedure, the analytic results of all psychological testing from the high school group closely mirrored those of the enlisted group, and college results matched those of the officer group, since, in general, the attainment of a college degree is a prerequisite for commissioning as an officer. However, 124 of the Ranch Hand enlisted and 98 of the original comparison enlisted personnel have college degrees as well. The similarities between these groups are graphically demonstrated in Figure XIII-1, where full scale IQ scores are compared. Since the variables of rank and education had identical impact on the analyses of psychological data, only the data from the educational analyses will be presented. The results of the rank analyses parallel those of education, and their presentation in this report would not further clarify the herbicide/dioxin issue.

Figure XIII-1

COMPARISON OF EDUCATIONAL ACHIEVEMENT AND RANK



1. Analysis of Questionnaire Data

a. Past History of Emotional or Psychological Illness

Detailed information concerning reported emotional or psychological illnesses was sought and, wherever possible, these illnesses were coded to the ICD-9-CM, 1980 edition. The unadjusted chi-square analyses of these data are presented in Table XIII-2. It is evident from these analyses that there were no statistically significant differences in the type of reported psychological illnesses between the Ranch Hand and either the entire comparison group or the subset of original comparison individuals.

Table XIII-2

DISTRIBUTION OF REPORTED PSYCHOLOGICAL ILLNESS BY TYPE OF ILLNESS

Type of Illness	Original Comparisons	Ranch Hand	Entire Group Comparison
Psychoses	4	6	4
Alcohol Dependence	2	5	7
Anxiety	4	9	5
Other Neuroses	6	16	9
	P = 0.91 (Original Comparisons vs. Ranch Hand)		P = 0.59 (Ranch Hand vs. Entire Group Comparison)

b. Psychological Indices

A further comparison of the responses to the psychological subsections of the questionnaire was performed. Responses to the questions addressing each psychological dimension were combined in an index equal to the number of positive responses for each dimension. Group differences in the distribution of questionnaire responses were tested by the Kolmogorov-Smirnov two-sample test, and the results are tabulated in Table XIII-3 and XIII-4. The isolation index was analyzed in a discrete fashion, adjusted for educational level. The data for this index are presented in Table XIII-5. When the responses to the isolation scale are dichotomized as equal or greater than 14 or less than 14, a relative risk of 1.97 is seen, with a 95% confidence interval of 1.14 to 3.58. The number of individuals analyzed in the depression index is reduced, since this is primarily an index of severity, and those individuals not reporting depression were excluded from the analysis.

Table XIII-3

QUESTIONNAIRE PSYCHOLOGICAL INDICES
(HIGH SCHOOL EDUCATION)

Index	Group	N	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Fatigue	Ranch Hand	573	15.33	6.24	< 0.001
	Comparison	430	13.64	5.52	
Anger	Ranch Hand	573	11.27	4.74	0.002
	Comparison	430	9.99	3.64	
Erosion	Ranch Hand	572	22.34	7.90	< 0.001
	Comparison	429	20.00	6.70	
Anxiety	Ranch Hand	555	24.62	8.67	< 0.001
	Comparison	419	21.91	7.73	
Depression (Severity)	Ranch Hand	141	5.79	3.15	0.89
	Comparison	60	5.30	2.85	

Table XIII-4

QUESTIONNAIRE PSYCHOLOGICAL INDICES
(COLLEGE EDUCATION)

Index	Group	N	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Fatigue	Ranch Hand	447	12.79	4.55	0.88
	Comparison	335	12.83	4.45	
Anger	Ranch Hand	447	9.55	3.09	0.71
	Comparison	335	9.46	3.08	
Erosion	Ranch Hand	448	20.12	5.80	0.94
	Comparison	336	19.90	5.54	
Anxiety	Ranch Hand	437	21.23	6.74	0.63
	Comparison	328	20.51	5.96	
Depression (Severity)	Ranch Hand	60	5.22	2.80	*
	Comparison	39	4.46	2.11	

*Data too sparse for valid analysis

When an unadjusted analysis of reported depression (yes, no) was performed, there was a statistically significant group difference (P=0.002) with the Ranch Handers reporting more depression then the comparisons. This is not necessarily inconsistent with the analysis of severity (P=0.89).

Table XIII-5

ISOLATION INDEX, ADJUSTED FOR EDUCATION

Group	Index Score						
	≤5	6-7	8-9	10-11	12-13	≥14	Total
Ranch Hand	16	81	535	269	91	48	1040
Comparison	3	75	425	200	49	18	770

P = 0.002

The questionnaire responses to the questions concerning fatigue, anger, erosion, anxiety, and depression were analyzed with the exposure index, using a general linear model. When Blacks and non-Blacks were combined, the anger index was observed to be suggestively associated with exposure (P = 0.13) in officers but not in either of the enlisted occupational strata. All other exposure analyses had P values in excess of 0.40.

Educational level is a major influence on responses to the psychological assessment portion of the questionnaire. The responses to these questions did not differ between college educated Ranch Handers and comparisons, but all indices except depression did differ significantly in the high school educated participants. These variables were all subjectively measured, and the specific subsets of questions were not validated. It is unclear from these data whether these differences reflect a herbicide effect unique to the largely high school educated enlisted group or an educationally related response to a highly emotional public issue. This difference may also be a reflection of post-Vietnam stress in the frontline Ranch Hand personnel in contrast to the reduced stress in the comparison group stationed in support areas of SEA.

2. Physical Examination Parameters

During the physical examination, the Cornell Index, the Minnesota Multiphasic Personality Inventory (MMPI), the Halstead-Reitan Battery and the Wechsler Adult Intelligence Scales were used to assess psychologic functioning. Again, results were comparable whether using rank or educational attainment as stratification variables, and only the educational analyses are presented.

a. Cornell Index

The Cornell Index is a subjective 10 to 15 minute self-administered inventory of neuropsychiatric symptoms and complaints. It has been standardized and is a widely used testing instrument. Grading of the responses to the Cornell results in an overall index and separate indices for each of the ten subelements of the instrument. A total index score of 8 or less is considered to be normal. The overall index scores for the Ranch Hand and comparison groups were contrasted using the Kolmogorov-Smirnov technique after stratification for educational level (Table XIII-6). High school educated participants demonstrated a highly significant group differential ($P < 0.001$) but the index scores in the college groups were not different.

Table XIII-6

ANALYSIS OF CORNELL INDEX BY GROUP
(KOLMOGOROV-SMIRNOV TWO-SAMPLE TEST)

Educational Level	Group	Mean Score	Standard Deviation	P Value
High School	Ranch Hand	9.21	10.35	< 0.001
	Comparison	6.44	7.79	
College	Ranch Hand	3.66	5.43	0.59
	Comparison	3.44	4.58	

The subelement scores were analyzed by log-linear techniques using 6 categories of response. These results are displayed in Table XIII-7, and the results of a similar analysis, using data from all available comparisons, are included as well. These results were all adjusted for educational level, since education was found to affect test scores in a highly significant manner ($P < 0.0001$). Categorical analysis of the subelements revealed significant group differences between the Ranch Handers and the original comparisons in all areas except depression and the neurocirculatory system (NCS). This finding in depression on the Cornell Index is inconsistent with the significant observation noted in the responses to the in-home questionnaire, and may reflect the presence of differential reporting. The NCS scores were suggestive of group differences with a P value of 0.12. Analysis of the entire comparison group revealed similar findings.

Table XIII-7

CATEGORICAL ANALYSIS OF GROUP DIFFERENCES IN THE CORNELL INDEX
(ADJUSTED FOR EDUCATION)*

Parameter	P Value: Ranch Hand Versus Original Comparisons	P Value: Ranch Hand Versus All Comparisons
Fear and Inadequacy	0.02	0.06
Depression	0.39	0.16
Nervousness and Anxiety	0.002	0.009
Neurocirculatory System	0.12	0.14
Startle	0.004	0.04
Psychosomatic	0.002	0.002
Hypochondria	0.05	0.12
Gastrointestinal System	0.01	0.01
Sensitivity	0.08	0.29
Troublesomeness	0.06	0.06

* All of these parameters were significantly affected by education level ($P < 0.0001$)

Analysis of the Ranch Hand group's overall Cornell Index by degree of exposure was performed, using log-linear techniques. The Cornell Index was compared with exposure level (low, medium, and high) and education (high school and college) after stratification for occupation. In each occupational category, the index was clearly influenced by educational level but not by degree of herbicide exposure. Table XIII-8 contains the results of these analyses.

Table XIII-8

EXPOSURE ANALYSIS OF THE CORNELL INDEX
(ADJUSTED FOR EDUCATIONAL LEVEL)

Occupational Category	P Value: Cornell Versus Exposure	P Value: Cornell Versus Education
Officer	0.91	0.09
Enlisted, flying	0.53	0.05
Enlisted, ground	0.26	0.04

Analysis of the overall Cornell Index identified significant group differences among high school-educated individuals ($P < 0.001$), with the Ranch Handers having a significantly higher mean (abnormal) score. However, this finding was not observed among the college educated individuals. Log-linear analyses of the Ranch Handers and original comparisons, adjusted for education, revealed significant differences in 6 of the 10 subscales of the index ($P \leq 0.05$) and borderline or suggestive findings in three others ($P \leq 0.12$). Despite these group differences, education adjusted exposure analysis of the overall Cornell Index did not identify any association between level of exposure and Cornell Index.

b. Minnesota Multiphasic Personality Inventory (MMPI)

The MMPI, a standardized set of 566 subjective self-administered questions concerning various aspects of behavior and personality, was completed by 1023 Ranch Handers, 767 original comparisons, and 1194 total comparisons. Scoring was performed by machine, using the standard criteria for normality of 30-70. The comparison of the distributional characteristics of the responses to each of the subelements of the MMPI are shown in Tables XIII-9 and XIII-10. The effect of educational level on psychological scores is again seen, with more suggestive and/or significant differences between groups appearing in the high school stratum. The validity scale was not different between Ranch Handers and comparisons in either educational stratum; however, the high school comparisons exhibited a greater degree of denial (K scale) than the high school Ranch Handers. Depression ($P = 0.16$), paranoia ($P = 0.19$) and hysteria scales ($P = 0.12$) were suggestive of group differences in the high school stratum and significant differences were noted in the masculinity/femininity, hypochondria, mania/hypomania, and social introversion scales, with comparisons faring better than the Ranch Handers. The college stratum demonstrated borderline significance in the masculinity/femininity scale ($P = 0.09$) and a significant difference ($P = 0.04$) in social introversion. The masculinity/femininity scale is heavily influenced by the range of interests held by the participants. As individuals increase their education and broaden their interests beyond traditional "male" activities, the score tends to rise (Lachar, 1974). This is demonstrated by the means of 57.87 to 59.15 in the college stratum and means of 54.85 to 55.94 in the high school group. The consistent finding of significance in social introversion, with the Ranch Handers being more inwardly directed, is striking, but its clinical relevance is unclear. The percent of the Ranch Handers and comparisons exhibiting abnormal MMPI scores (greater than 70 or less than 30) are shown in Table XIII-11 for those scales with suggestive or significant findings.

The increased score on the denial (K) scale of the MMPI for the enlisted comparison group may be an indication of a relative differential in reporting between the two groups. When considered in the light of an increased enlisted Ranch Hand hypochondria scale on both the Cornell Index and the MMPI, overreporting in the Ranch Hand group is indicated.

Table XIII-9

ANALYSIS OF MMPI TESTING IN HIGH SCHOOL-EDUCATED PARTICIPANTS
(RANCH HAND N = 575; COMPARISON N = 430)

Parameter	Group	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Validity	Ranch Hand	1.85	4.54	0.99
	Comparison	1.73	4.07	
Defensiveness (L Scale)	Ranch Hand	51.99	7.84	0.98
	Comparison	52.03	8.15	
Consistency (F Scale)	Ranch Hand	51.95	9.29	0.44
	Comparison	50.65	7.16	
Denial (K Scale)	Ranch Hand	53.95	8.86	0.03*
	Comparison	55.63	8.12	
Hypochondria	Ranch Hand	59.74	13.36	0.05
	Comparison	57.22	10.95	
Depression	Ranch Hand	60.47	13.98	0.16
	Comparison	58.39	11.96	
Hysteria	Ranch Hand	60.12	9.96	0.12
	Comparison	58.90	8.23	
Psychopathic/Deviate	Ranch Hand	56.38	11.00	0.86
	Comparison	55.89	10.52	
Masculinity/Femininity	Ranch Hand	55.94	8.32	0.01
	Comparison	54.85	8.94	
Paranoia	Ranch Hand	51.72	8.66	0.19
	Comparison	50.68	8.33	
Psychasthenia (Anxiety)	Ranch Hand	57.27	12.23	0.47
	Comparison	55.59	10.07	
Schizophrenia	Ranch Hand	57.53	13.42	0.45
	Comparison	55.97	9.71	
Mania/Hypomania	Ranch Hand	56.03	10.36	0.01
	Comparison	54.49	10.31	
Social Introversion	Ranch Hand	52.31	10.38	0.006
	Comparison	50.80	9.50	

*Comparisons greater than Ranch Hand

Table XIII-10

ANALYSIS OF MMPI TESTING IN COLLEGE-EDUCATED PARTICIPANTS
(RANCH HAND N = 448; COMPARISON N = 337)

Parameter	Group	Mean Score	Standard Deviation	Kolmogorov-Smirnov P Value
Validity	Ranch Hand	1.48	4.14	0.47
	Comparison	1.95	4.49	
Defensiveness (L Scale)	Ranch Hand	50.26	7.68	0.99
	Comparison	50.33	7.29	
Consistency (F Scale)	Ranch Hand	48.74	5.84	0.99
	Comparison	48.44	5.36	
Denial (K Scale)	Ranch Hand	58.46	7.53	0.99
	Comparison	58.41	7.64	
Hypochondria	Ranch Hand	55.42	9.34	0.96
	Comparison	54.65	8.45	
Depression	Ranch Hand	55.34	10.77	0.99
	Comparison	54.57	9.98	
Hysteria	Ranch Hand	59.75	7.38	0.98
	Comparison	59.32	7.01	
Psychopathic/Deviate	Ranch Hand	55.21	9.33	0.68
	Comparison	55.66	8.90	
Masculinity/Femininity	Ranch Hand	59.15	8.72	0.09
	Comparison	57.87	8.98	
Paranoia	Ranch Hand	53.62	6.96	0.63
	Comparison	53.26	6.64	
Psychasthenia (Anxiety)	Ranch Hand	53.62	8.04	0.84
	Comparison	54.18	8.36	
Schizophrenia	Ranch Hand	54.70	7.94	0.79
	Comparison	54.89	7.88	
Mania/Hypomania	Ranch Hand	55.22	9.55	0.51
	Comparison	54.05	10.03	
Social Introversion	Ranch Hand	46.83	8.67	0.04
	Comparison	47.50	7.98	

Table XIII-11

MMPI ABNORMALITY BY GROUP

Level	MMPI Scale	Group	% Below 30	% Above 70
High School	Denial	Ranch Hand	0.0	1.7
		Comparison	0.0	3.7
	Hypochondria	Ranch Hand	0.0	18.1
		Comparison	0.0	10.9
	Depression	Ranch Hand	0.2	18.1
		Comparison	0.0	12.2
	Hysteria	Ranch Hand	0.0	14.1
		Comparison	0.0	7.9
	Masculinity/ Femininity	Ranch Hand	0.0	4.5
		Comparison	0.0	5.6
	Paranoia	Ranch Hand	0.0	2.4
		Comparison	0.0	1.9
	Mania/Hypomania	Ranch Hand	0.3	8.5
		Comparison	0.2	8.6
	Social Intro- version	Ranch Hand	0.0	6.8
		Comparison	0.0	4.9
College	Masculinity/ Femininity	Ranch Hand	0.0	11.6
		Comparison	0.0	11.0
	Social Intro- version	Ranch Hand	0.0	1.6
		Comparison	0.3	1.8

Log-linear analysis of the MMPI data, using dichotomous (normal/abnormal) responses was also conducted (Table XIII-12). Educational level was again found to exert a highly significant influence in all scales, with P values all less than 0.01.

Table XIII-12

LOG-LINEAR ANALYSIS OF THE MMPI SCALES BY GROUP
(ADJUSTED FOR EDUCATION)

Scale	P Value of Group Difference
Hypochondria	< 0.001
Depression	0.02
Hysteria	0.002
Psychopathic/Deviate	0.39
Masculinity/Femininity	0.84
Paranoia	0.26
Psychasthenia	0.21
Schizophrenia	0.007
Mania/Hypomania	0.52
Social Introversion	0.32

Several of these analyses appear to be inconsistent with the results of the Kolmogorov-Smirnov testing, making inference more difficult. Most of the statistically significant group differences found in the distributional analyses were in the high school group, but the log-linear analysis revealed highly significant group differences (P = 0.02) between the Ranch Hand and comparison groups after adjustment for education. Matched pair analyses, using the original comparison subset, were conducted on the hysteria, hypochondria, and masculinity/femininity scales, with respective P values of 0.02, 0.02, and 0.66. These results mirror those of the log-linear analysis in Table XIII-12.

The initial group analyses of the MMPI were performed without consideration for the variable of race. A repeat analysis of MMPI scores was also conducted for the 63 Ranch Handers and 45 originally selected comparisons who were Black. The results of this analysis are presented in Table XIII-13. Wherever the sample size permitted, the analyses were adjusted for education; however, sparseness of data prevented adjustment in the analysis of the psychasthenia, schizophrenia, and masculinity/femininity scales and prevented any analysis for the paranoia and social introversion scales. The borderline significant finding in the schizophrenia scale (P = 0.07) is somewhat parallel to the significant P value for schizophrenia (P = 0.007) in Table XIII-12. These findings do not suggest that the factor of race is at all responsible for the overall differences in MMPI scores between the Ranch Hand and comparison groups.

Table XIII-13

MMPI ANALYSIS AMONG BLACK PARTICIPANTS

Scale	Adjusted for Education	P Value of Group Difference
Hypochondria	Yes	0.15
Depression	Yes	0.91
Hysteria	Yes	0.31
Psychopathic/Deviate	Yes	0.73
Mania/Hypomania	Yes	0.70
Psychasthenia	No	0.20
Schizophrenia	No	0.07
Masculinity/Femininity	No	0.31
Paranoia	N/A	-
Social Introversion	N/A	-

Exposure analysis of the Ranch Hand group, using log-linear techniques revealed a mixed pattern of significant, borderline and suggestive findings. These results are summarized in Table XIII-14. Education remains a significant factor, but consistency across occupational groups is not evident, since stratification by occupational group mirrored stratification by education. Table XIII-15 displays the exposure index data, and the percentage of abnormal MMPI scale results, for the exposure analyses with P values of concern. Only the hysteria scale in the officers attending college and the psychopathic deviate scale in both high school and college officers showed consistent increases in abnormality with increasing exposure. However, the number of abnormal scores in all of these scales was quite low and inferential accuracy is compromised.

Table XIII-14

P VALUES OF THE MMPI/EXPOSURE ANALYSES (ADJUSTED FOR EDUCATION)

	P Value Parameter Versus Exposure			P Value Parameter Versus Education		
		Enlisted			Enlisted	
Parameter	Officer	Flying	Ground	Officer	Flying	Ground
Hypochondria	0.21	0.97	0.02	0.18	0.10	0.03
Depression	0.70	0.11	0.16	0.46	0.12	0.27
Hysteria	0.21**	0.76	0.0005	0.34	0.62	0.04
Psychopathic Deviate	0.001*	1.00	0.15	0.17	0.20	0.16
Masculinity/Femininity	0.09	0.81	0.09	0.28	0.04	0.005
Paranoia	1.00	0.64	0.53	0.72	0.83	0.20
Psychasthenia	0.89	0.05	0.48	0.29	0.56	0.07
Schizophrenia	0.09	0.12	0.73	0.43	0.50	0.03
Mania/Hypomania	0.32	0.13	0.29	0.86	0.81	0.41
Social Introversion	0.39	0.33	0.78	0.77	0.93	0.02

*Significant confounding by education present
**Significant three-way interaction present

Table XIII-15

DOSE RESPONSE PATTERNS

Parameter	Group	Exposure Level	Number Normal	Number Abnormal (%)
Hypochondria	Enlisted Ground	Low	110	38 (25.7%)
		Medium	153	25 (14.0%)
		High	119	29 (19.6%)
Depression	Enlisted Flying	Low	48	10 (17.2%)
		Medium	41	18 (30.5%)
		High	55	11 (16.7)
	Enlisted Ground	Low	111	37 (25.0%)
		Medium	148	30 (16.9%)
		High	119	29 (19.6%)
Hysteria*	Officers (High School)	Low	10	0 (0%)
		Medium	14	5 (26.3%)
		High	24	0 (0%)
	Officers (College)	Low	97	3 (3.0%)
		Medium	104	5 (4.6%)
		High	91	9 (9.1%)
	Enlisted Ground	Low	115	33 (22.3%)
		Medium	163	15 (8.4%)
		High	132	16 (10.8%)
Psychopathic/Deviate*	Officers (High School)	Low	10	0 (0%)
		Medium	19	0 (0%)
		High	23	1 (4.2%)
	Officers (College)	Low	100	0 (0%)
		Medium	102	7 (6.4%)
		High	90	10 (10%)
	Enlisted Ground	Low	127	21 (14.2%)
		Medium	164	14 (7.9%)
		High	131	17 (11.5%)
Masculinity/Femininity	Officers	Low	105	5 (4.5%)
		Medium	113	15 (11.7%)
		High	111	13 (10.5%)
	Enlisted Ground	Low	135	13 (8.8%)
		Medium	172	6 (3.4%)
		High	136	12 (8.1%)
Psychasthenia	Enlisted Flying	Low	54	4 (6.9%)
		Medium	48	11 (1.9%)
		High	62	4 (6.1%)
Schizophrenia	Officers	Low	108	2 (1.8%)
		Medium	119	9 (7.0%)
		High	121	3 (2.4%)
	Enlisted Flying	Low	55	3 (5.2%)
		Medium	49	10 (16.9%)
		High	59	7 (10.6%)
Mania/Hypomania	Enlisted Flying	Low	53	6 (10.2%)
		Medium	50	9 (15.3%)
		High	63	3 (4.8%)

*Data are presented by educational level when the education/exposure interactions are statistically significant.

Analysis of the MMPI data from the Ranch Hand and original comparison groups revealed significant group differences in the hypochondria, depression and hysteria scales ($P \leq 0.02$), after adjustment for education. Stratified analysis based on level of education revealed statistically significant group differences for the hypochondria and masculinity/femininity scales ($P \leq 0.05$). However, there were no statistically significant group differences among college-educated individuals, and only in the masculinity/femininity scale was borderline significance reached ($P = 0.09$). Exposure analyses did not reveal any consistent patterns of statistical significance between occupational categories, level of exposure and MMPI scores.

c. Halstead-Reitan

The Halstead-Reitan Neuropsychological Test Battery was administered to each participant to assess the functional integrity of the central nervous system. An impairment index for each participant was calculated based upon the scores of the category, tactual performance, speech-sounds, Seashore rhythm, and finger-tapping portions of the battery. The impairment index ranged from zero to seven, based on the number of subtests in which the participant scored abnormally. Impairment was declared if the index equalled or exceeded three. Larger numbers of participants were deleted from these analyses; since seven distinct tests contributed to the impairment index. The absence of any one made calculation of the index impossible. Analysis of dicotomous variables (normal/abnormal), adjusted for education, revealed no overall group differences ($P = 0.74$).

A categorical analysis, unadjusted for educational level, was performed. The data and the results of the unadjusted analyses of the Ranch Hand group, the entire comparison group and the subset of original participants are presented in Table XIII-16.

Table XIII-16

UNADJUSTED HALSTEAD-REITAN SCORES BY GROUP

Impairment Index	Original Comparisons N = 559		Ranch Hand N = 771		All Comparisons N = 883	
0	85		124		141	
1	162	66.5%*	226	66.5%*	248	66.0%*
2	125		163		194	
3	77		126		134	
4	60		68		85	
5 or more	50		64		81	

Original Comparisons vs. Ranch Hand: $x^2 = 3.18$, $P = 0.67$

Ranch Hand vs. All Comparisons: $x^2 = 1.35$, $P = 0.93$

* Cumulative % for Impairment Index 0,1,2

Analyses adjusted for education were carried out on the Ranch Handers and the original subset of comparisons (Table XIII-17). Education was again seen to be a significant factor ($P < 0.0001$).

Table XIII-17

HALSTEAD-REITAN ANALYSIS BY GROUP AND EDUCATION

Educational Level	Group	Degree of Impairment 0	1	2	3	4	5 or Greater
High School	Ranch Hand	45	108	88	80	54	56
	Comparison	29	69	69	49	38	37
College	Ranch Hand	79	118	75	46	14	8
	Comparison	56	93	56	28	22	13

P Value, adjusted for education = 0.57

An exposure index analysis was also accomplished on the data from the Ranch Hand group. As shown in Table XIII-18, educational level was a significant covariable in the officer and enlisted flying groups, but there were no significant relationships between herbicide exposure and Halstead-Reitan performance.

Table XIII-18

HALSTEAD-REITAN IMPAIRMENT AND EXPOSURE

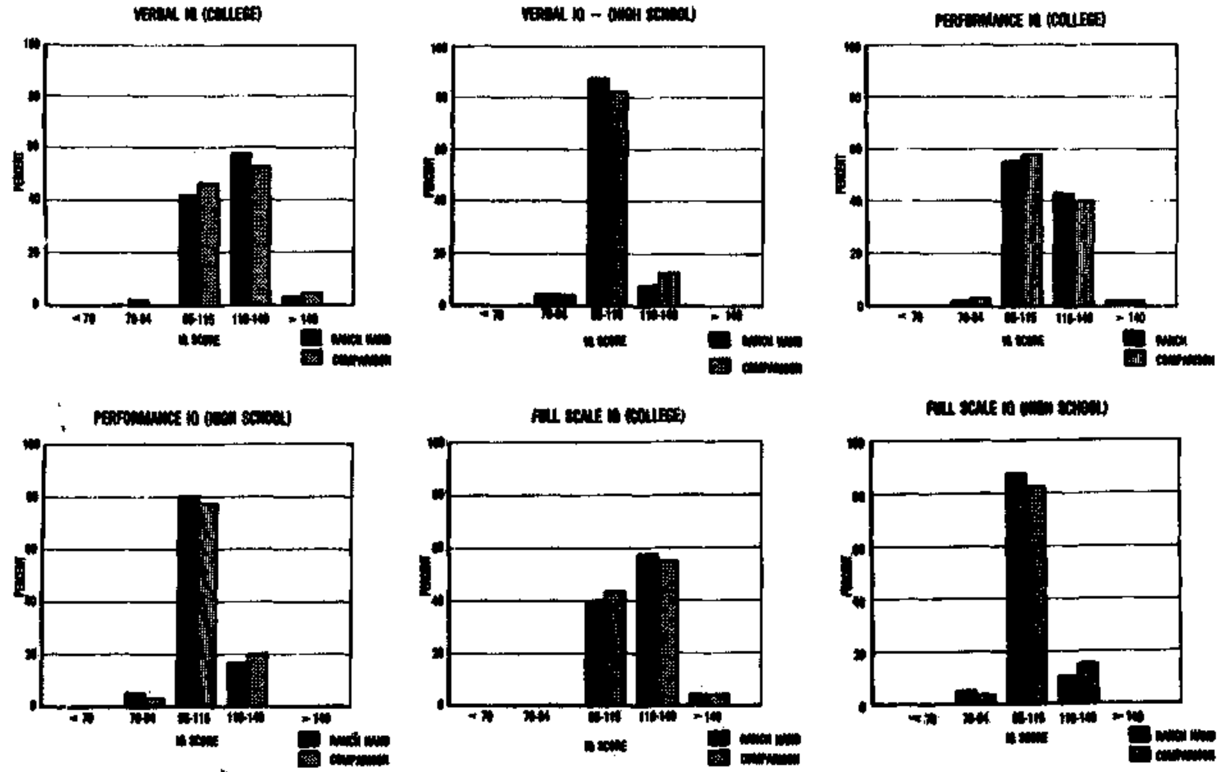
Occupational Group	Adjusted P Values: Halstead-Reitan Versus Exposure	Halstead-Reitan Versus Education
Officers	0.88	0.002
Enlisted Flying	0.44	0.05
Enlisted Ground	0.82	0.62

d. Wechsler Adult Intelligence Scale (WAIS)

WAIS testing was completed on 1022 Ranch Handers and 733 original comparison individuals. The test was administered and scored in the standard manner by certified clinical psychologists and psychological technicians. As noted previously, intelligence scores (IQ) by rank were equivalent to IQ scores by education. The distributions of verbal, performance and full-scale IQ scores, by educational level and group, are shown in Figure XIII-2.

Figure XIII-2

FREQUENCY DISTRIBUTION IQ SCORES BY EDUCATIONAL LEVEL AND GROUP



The IQ scores demonstrated consistent patterns within each educational stratum. A slight increase in the proportion of both Ranch Hand and comparison college graduates, with performance IQ's between 85 and 115, was noted. These distributions were tested for group differences by the Kolmogorov-Smirnov procedure. Suggestive but nonsignificant differences were noted for performance and full-scale IQ's in the high school stratum, but no differences were found among the college-educated group. These data are shown in Table XIII-19.

Table XIII-19

DISTRIBUTIONAL ANALYSIS OF IQ SCORES

Scale	Education	Group	Mean Score	Standard Deviation	P Value
Verbal	High School	Ranch Hand	110.61	10.65	0.39
		Comparison	101.73	11.34	
	College	Ranch Hand	117.00	12.97	0.73
		Comparison	116.84	13.73	
Performance	High School	Ranch Hand	102.40	11.38	0.14
		Comparison	104.14	11.86	
	College	Ranch Hand	113.70	12.62	0.50
		Comparison	112.37	13.33	
Full Scale	High School	Ranch Hand	101.18	10.71	0.15
		Comparison	102.74	11.32	
	College	Ranch Hand	117.30	12.96	0.37
		Comparison	116.59	13.82	

The distributions were observed to identify outliers, and the percentage of participants with scores in the abnormal range (below 85) was determined. These results are shown in Table XIII-20.

Table XIII-20

ABNORMAL IQ SCORE BY GROUP AND EDUCATIONAL LEVEL

Educational Level	Scale	Group	% Below 85	% Above 115
High School	Verbal	Ranch Hand	3.7	9.8
		Comparison	3.3	13.7
	Performance	Ranch Hand	5.4	14.3
		Comparison	3.7	18.8
	Full	Ranch Hand	4.0	10.6
		Comparison	3.5	15.1
College	Verbal	Ranch Hand	0.9	58.8
		Comparison	0.3	54.1
	Performance	Ranch Hand	1.1	43.9
		Comparison	1.8	41.1
	Full	Ranch Hand	0.7	61.1
		Comparison	0.3	56.2

Analysis of the WAIS testing scores of the Ranch Hand group, by level of herbicide exposure, revealed no consistent differences in IQ scores. The P values derived from these analyses are presented in Table XIII-21 and show only one statistically significant association (P = 0.04).

Table XIII-21

RESULTS OF IQ SCORES BY EXPOSURE ANALYSIS

Scale	Occupational Group	P Value
Verbal	Officers	0.99
	Enlisted Flying	0.34
	Enlisted Ground	0.82
Performance	Officers	0.99
	Enlisted Flying	0.04
	Enlisted Ground	0.18
Full Scale	Officers	0.99
	Enlisted Flying	0.23
	Enlisted Ground	0.25

2. Summary

In this chapter, a large number of variables were analyzed using several techniques and multiple assessments. Consistent differences between high school-educated Ranch Handers and high school-educated original comparisons are seen throughout these analyses. With the exception of a single statistically significant result for social introversion (P = 0.04), these group differences are not apparent in the college educated stratum. Unstratified but educationally adjusted analyses of the MMPI scores did, however, reveal group differences which were more like those of the high school stratum. Exposure analyses did not reveal any patterns suggesting any association between psychological testing results and level of herbicide exposure. The relative risks, confidence intervals, and shifts in means for the dependent variables analyzed in this chapter are included in Appendix XVIII.

Table XIII-22

PSYCHOLOGICAL ANALYSIS SUMMARY
(RANCH HAND VERSUS ORIGINAL COMPARISON GROUP)

	Analytic Strategy (P Values)					
	Adjusted for	Stratified Analysis		Exposure Analysis		
Parameter	Education	High School	College	Off	Enl Fly	Enl Gnd
Questionnaire Indices						
Fatigue		<0.001	NS*			
Anger		0.002	NS			
Erosion		<0.001	NS			
Anxiety		<0.001	NS			
Isolation	0.002					
Depression (Severity)		0.89				
Cornell Index		<0.001	NS	NS	NS	NS
Fear and Inadequacy	0.02					
Depression	NS					
Nervousness and Anxiety	0.002					
Neurocirculatory	0.12					
Startle	0.004					
Psychosomatic	0.002					
Hypochondria	0.05					
Gastrointestinal	0.01					
Sensitivity	0.08					
Troublesomeness	0.06					
MMPI						
Hypochondria	<0.001	0.05	NS	NS	NS	0.02
Depression	0.02	0.16	NS	NS	0.11	0.16
Hysteria	0.002	0.12	NS	NS	NS	0.001
Psychopathic Deviate	NS	NS	NS	0.001	NS	0.15
Masculinity/Femininity	NS	0.01	0.09	0.09	NS	0.09
Paranoia	NS	0.19	NS	NS	NS	NS
Psychasthenia	NS	NS	NS	NS	0.05	NS
Schizophrenia	0.007	NS	NS	0.09	0.12	NS
Mania/Hypomania	NS	0.01	NS	NS	0.13	NS
Social Introversion	NS	0.006	0.04	NS	NS	NS
Halstead-Reitan	NS			NS	NS	NS
IQ Scores						
Verbal		NS	NS	NS	NS	NS
Performance		0.14	NS	NS	0.04	0.18
Full Scale		0.15	NS	NS	NS	NS

*Nonsignificant; P > 0.20

The results of the analyses of the psychological data are summarized in Table XIII-22, and demonstrate a greater degree of statistically significant group differences in the more subjective measurements (questionnaire and Cornell Index) than are observed in the more objective assessments (Halstead-Reitan and WAIS). The effect of differential reporting in this evaluation is as yet difficult to assess. However, the high school-educated Ranch Handers did have higher scores on the hypochondria scale of the MMPI and the psychosomatic portion of the Cornell Index than did the appropriate comparisons. Additionally, the high school-educated comparisons scored higher on the MMPI K Scale (denial). These findings suggest that differential reporting may be influencing the analytic results of the in-home questionnaire and the Cornell Index. There may also be a differential response to the intense media interest in the herbicide/dioxin issue between the high school and college strata in this study. The role of "Post Vietnam Stress" in these findings is also unclear at this time. Further clarification of these factors and their impact must await analysis of the data from the follow-up phase of the study. Based on the psychological data collected during the initial in-home questionnaire and physical examination, there is no convincing evidence suggesting the presence of an adverse effect on emotional health caused by herbicide exposure.

Chapter XIV

EVALUATION OF HEPATIC STATUS

1. Introduction

A very broad spectrum of hepatic phenomena has been reported in association with acute, subacute and chronic administration of TCDD to animals. Significant response differences between species occur, however. Serum enzyme changes (SGOT, SGPT, GGPT, LDH) have not been prominent, although SGPT levels were elevated in at least 1 study (Schantz et al, 1979). Elevated alkaline phosphatase levels have been observed with increased direct bilirubin levels (Kociba et al, 1976). Decreased serum cholesterol levels have also been noted after sublethal exposures (Schantz et al, 1979). TCDD interferes with hemoglobin metabolism affecting delta-aminolevulinic acid synthetase activity (Goldstein et al, 1973) and possibly other enzyme activities, providing, at sufficient doses, signs and symptoms of porphyria.

Motivated by the literature reports of hepatotoxicity, signs and symptoms of hepatic dysfunction were sought in the participants in this study. In this chapter, enzyme levels, bilirubin levels and lipid values are presented, along with determinations reflecting porphyrin metabolism. Clinical history data are also analyzed, along with hepatomegaly determined at physical examination.

2. Biochemical Determinations

a. Analyses Overview

In this section 9 biochemical determinations are studied: SGOT, SGPT, GGPT, alkaline phosphatase (Alk. Phos.), total bilirubin (T. Bili), direct bilirubin (D. Bili), lactic dehydrogenase (LDH), cholesterol (Chol) and triglycerides (Trig). These 9 variables are listed in Table XIV-1, along with the normal-abnormal ranges used in the reported statistical analyses. These ranges were adapted from Kelsey-Seybold laboratory normal ranges.

In the analyses of these 9 variables, adjustments were made for 4 covariates: current alcohol ingestion (ALC), days of exposure to industrial chemicals (IC), days of exposure to degreasing chemicals (DC), and presence or absence of antibody to hepatitis B surface antigen (anti-HB_SAg). The current alcohol use covariate was taken from the personal medical history administered at the time of the physical examination and is in units of average drinks per day (see Appendix VI, page 2). Current alcohol ingestion was selected as an adjusting variable over the drink years measure developed from the questionnaire, since preliminary testing indicated it correlated better with hepatic endpoints. The industrial chemical and degreasing chemical exposures were derived from the in-home questionnaire (total unprotected exposure).

The data analyzed were from the entire Ranch Hand cohort compliant to the physical examination (N = 1045) and the original comparisons compliant to the physical examination (N = 773). Ten Ranch Handers and 2 comparisons were removed from the analysis because of body temperature of 100°F or more, and the effect of fever on hepatic variables. Individuals whose blood contained hepatitis B surface antigen (HB_SAg) were also removed from the analysis (8 Ranch Handers and 7 comparisons).

b. Group Analyses

Three sets of analyses were run:

(1) Continuous-continuous analyses (CC): In these evaluations both the dependent variables and adjusting covariates, except anti-HB_SAg which is dichotomous, were used as continuous variables in an analysis of covariance.

(2) Continuous-discrete analyses (CD): In these analyses all 4 covariates were used as dichotomous variables while the dependent variables were maintained as continuous.

(3) Discrete-discrete analyses (DD): All variables were analyzed in dichotomous form using the log-linear model for discrete data.

In all 3 analysis settings, group-by-covariate interactions were examined. In addition, the continuous-continuous and continuous-discrete analyses models were fit without interaction terms to provide discussion of appropriate tests when dependent variable relationships with the covariates are the same in both groups. In the continuous-continuous and continuous-discrete analyses the dependent variable was normalized by using a logarithmic (base 10) transformation.

Table XIV-1

NORMAL - ABNORMAL LEVELS OF NINE BIOCHEMICAL DETERMINATIONS REFLECTING HEPATIC FUNCTION

Determination	Normal	Abnormal
1. SGOT	≤ 41	> 41
2. SGPT	≤ 45	> 45
3. GGPT	≤ 85	> 85
4. Alkaline Phosphatase	≤ 9.7	> 9.7
5. Total Bilirubin	≤ 1.2	> 1.2
6. Direct Bilirubin	≤ 0.36	> 0.36
7. Lactic Dehydrogenase	≤200	>200
8. Cholesterol	≤240	>240
9. Triglycerides	≤150	>150

Table XIV-2 provides unadjusted means, adjusted means, and percent abnormality by groups for the 9 hepatic-related variables. A summary of the 3 classes of analyses is provided in Table XIV-3. The results in this table provide P values for Ranch Hand-comparison group differences.

Table XIV-2

UNADJUSTED MEANS, ADJUSTED MEANS AND PERCENT ABNORMALITY FOR NINE LIVER-RELATED VARIABLES

Variable	Group	Unadjusted Means	Adjusted Means	Percent Abnormality
SGOT	RH	33.0	33.0	13.9
	COM*	33.1	33.1	14.8
SGPT	RH	20.3	20.3	7.8
	COM	20.5	20.5	8.6
GGPT	RH	40.2	40.1	10.8
	COM	39.3	39.3	10.3
Alk. Phos.	RH	7.68	7.69	17.3
	COM	7.53	7.52	16.9
T. Bili	RH	0.57	0.57	1.8
	COM	0.58	0.58	2.0
D. Bili	RH	0.23	0.23	29.0
	COM	0.24	0.24	29.7
LDH	RH	142.1	142.1	1.7
	COM	141.7	141.7	2.1
CHOL	RH	212.2	212.2	26.0
	COM	216.6	216.6	27.7
TRIG	RH	121.8	121.9	34.7
	COM	124.3	124.1	36.1

*COM denotes original fully compliant comparisons.

Table XIV-3

SUMMARY OF RESULTS
UNMATCHED ANALYSES OF NINE BIOCHEMICAL VARIABLES REFLECTING LIVER FUNCTION

		P Values for Models with Interaction									P Values for models without Interaction				
VAR	ANAL	Gp	ALC	IC	DC	anti HB_sAg	Gp X ALC	Gp X IC	Gp X DC	Gp X anti HB_sAg	Gp	ALC	IC	DC	anti HB_sAg
SGOT	CC	.127	<.001	-*	-	-	.032	-	-	-	.805	<.001	-	-	-
	CD	.278	<.001	-	-	-	-	-	-	-	.867	<.001	-	-	-
	DD	.578	<.001	-	-	-	-	-	-	-					
SGPT	CC	.736	<.001	-	-	-	-	-	-	-	.663	<.001	-	-	-
	CD	.309	.005	-	-	-	-	-	-	-	.662	.003	-	-	-
	DD	.592	-	-	-	-	-	.052	-	-					
GGPT	CC	.731	<.001	-	-	-	-	-	-	-	.483	<.001	-	-	-
	CD	.050	<.001	-	-	.066	-	-	-	-	.421	<.001	-	-	.078
	DD	.782	<.001	-	-	-	-	-	-	-					
ALK PHOS	CC	.405	-	-	-	.009	-	-	-	-	.140	-	.071	-	.009
	CD	.142	.001	-	-	.010	-	-	-	-	.115	.001	.066	-	.011
	DD	.734	-	-	-	-	-	-	-	-					
TOT BILI	CC	.113	.014	.036	.001	.100	-	-	-	-	.423	.009	.011	<.001	.095
	CD	.606	-	-	-	-	-	-	-	-	.400	-	-	-	.099
	DD	.800	-	-	-	.027	-	-	-	-					
DIR BILI	CC	.494	.004	-	.032	-	-	-	-	-	.770	.003	-	.016	-
	CD	.371	.091	-	-	-	.069	-	-	-	.755	-	-	-	-
	DD	.869	-	-	-	-	-	-	-	-					
LDH	CC	.063	.090	-	-	-	.011	-	.037	-	.836	.025	-	.023	-
	CD	.024	-	-	-	-	-	-	-	-	.711	-	-	-	-
	DD	.526	-	-	-	-	.086	-	-	-					
CHOL	CC	.062	<.001	.079	-	-	-	-	-	-	.022	<.001	.061	-	-
	CD	.216	.014	-	-	-	-	-	-	-	.031	.020	-	-	-
	DD	.466	.053	-	-	-	-	-	-						
TRIG	CC	.911	-	-	-	-	-	-	-	-	.601	-	-	-	-
	CD	.284	-	-	-	-	-	-	-	-	.616	-	-	-	-
	DD	.589	-	-	-	-	-	-	-	-					

* - denotes P > 0.050 for main effects, P > 0.100 for interation effects

In Tables XIV-2 and XIV-3, there is a very slight indication of overall group differences in the GGPT with the Ranch Hand mean greater than the comparison mean and a P value of 0.050 in the CD analysis with interaction terms. However, when interaction terms are not considered, P = 0.421. This may indicate some interaction effects even though they were not detected as statistically significant. Additionally, no difference is detected in the CC or DD analyses. A stronger indication of overall group difference is seen with LDH; however, it is interesting to note that while the Ranch Hand mean LDH is greater than the comparison mean, the Ranch Hand percent abnormal LDH is less than that of the comparison group. The Ranch Hand cholesterol mean is lower than that of the comparison group and the result appears unlikely to have occurred by chance (P value of 0.062 in the full model CC analysis; P values of 0.022 and 0.031 in the CC and CD analyses respectively not using interaction terms). These group differences in GGPT, LDH and CHOL are all small.

Further group specific differences are noted in interaction effects with covariables. Ranch Hand SGOT levels are correlated more highly with alcohol ingestion than are comparison SGOT levels. The Ranch Hand SGOT - alcohol regression slope is 0.0178 logarithmic units per drink per day, while the comparison SGOT - alcohol slope is 0.0113 logarithmic units per drink per day. This difference in slopes is statistically significant with P = 0.032, and could represent differing hepatic sensitivities to alcohol.

A borderline group by industrial chemical exposure is noted in the DD analysis of SGPT levels. This interaction is shown in Table XIV-4.

Table XIV-4

INDUSTRIAL CHEMICAL EXPOSURE AND % ABNORMAL SGPT IN RANCH HAND AND COMPARISON GROUPS

	Ranch Hand	Comparison
Exposure	8.84% (38 of 430)	6.71% (23 of 343)
No Exposure	7.19% (42 of 584)	10.1% (42 of 416)

Ranch Hand personnel exposed to industrial chemicals have a higher proportion of abnormal SGPT values than do Ranch Hand personnel who are not exposed to industrial chemicals. The situation is reversed in the comparison group. The relative risk for abnormal SGOT in the Ranch Hand group associated with industrial chemical exposure is 1.23, while the comparison relative risk is 0.66, and this difference carries a P value of 0.052.

Two group-by-covariate interactions are noted in the LDH data. In the comparison group neither alcohol ingestion nor exposure to degreasing chemicals was associated with change in LDH levels, while in the Ranch Hand group, increased levels were noted to occur in association with both exposures. Specifically, in the comparison group the LDH-alcohol slope is -0.0008 logarithmic units per drink per day which is not statistically significantly different from zero ($P = 0.577$). Also, the comparison LDH-degreasing chemical slope is -0.08×10^{-5} units per exposure day ($P = 0.735$ against the null hypothesis of zero slope). On the other hand, the Ranch Hand LDH-alcohol slope is 0.0041 units per drink per day ($P < 0.001$ against hypothesis of zero slope) and the LDH-degreasing slope is 0.51×10^{-5} units per exposure day ($P = 0.003$ against zero slope hypothesis).

c. Exposure Analyses

Analyses within the Ranch Hand cohort are presented contrasting the hepatic clinical variables against the herbicide exposure index. For this exposure index work, separate analyses were run for each of 3 occupational groups: officers, enlisted flying and enlisted ground. The 9 hepatic variables were analyzed as continuous dependent variables after logarithmic transformation. As with the Ranch Hand-comparison group analyses, alcohol use, industrial chemical exposure, degreasing chemical exposure and antibody to Hepatitis B surface antigen were used as adjusting covariates, and individuals with body temperature greater than or equal to 100°F were omitted from the analysis as were individuals with hepatitis B surface antigen. For this exposure index effort, alcohol use, industrial chemical exposure and degreasing chemical exposure were used as continuous variables.

Table XIV-5 is a display of exposure means adjusting for covariates without invoking interaction. Table XIV-6 provides a summary of P values for the testing. Analyses of covariance or generalized linear models with and without interaction were employed.

An overall or main exposure effect on GGPT levels is indicated among officers and enlisted ground personnel. However, clear-cut dose-response patterns are not noted, rather, in the officer cohort the medium exposure subgroup has the highest mean GGPT while in the enlisted ground cohort the subgroup with low exposure has the highest GGPT.

Six exposure group-by-covariate interactions were found at $P \leq 0.050$. These interactions are written out in Table XIV-7. In this table, the slope of the dependent variable with respect to the covariate of interest is provided for each of the 3 exposure levels.

An exposure-by-degreasing chemical interaction was noted in SGOT in officers. Low herbicide exposure is associated with a possible depression of SGOT levels with increasing degreasing chemical exposure, while individuals in the high herbicide exposure group show increasing SGOT levels with increasing degreasing chemical exposure.

Table XIV-5

ADJUSTED BIOCHEMICAL MEANS BY EXPOSURE AND OCCUPATIONAL CATEGORY, WITH TYPICAL SAMPLE SIZES

Variable	Occupational Category	Low Exposure	Medium Exposure	High Exposure
SGOT	Officer	33.3	32.2	33.0
	Enl. F.	31.8	33.5	31.7
	Enl. G.	33.6	32.7	34.1
SGPT	Officer	20.2	19.9	19.4
	Enl. F.	18.5	20.8	18.4
	Enl. G.	21.3	21.1	20.6
GGPT	Officer	37.1	39.5	37.5
	Enl. F.	41.4	45.9	37.8
	Enl. G.	43.0	40.2	40.5
Alk. Phos.	Officer	6.91	7.24	7.47
	Enl. F.	8.13	7.88	7.98
	Enl. G.	7.93	7.85	8.04
T. Bili.	Officer	0.56	0.55	0.57
	Enl. F.	0.53	0.56	0.54
	Enl. G.	0.58	0.58	0.60
D. Bili.	Officer	0.22	0.23	0.23
	Enl. F.	0.18	0.23	0.21
	Enl. G.	0.25	0.24	0.26
LDH	Officer	141.3	139.4	139.3
	Enl. F.	143.1	141.0	149.3
	Enl. G.	142.9	140.8	144.9
Chol.	Officer	214.6	213.0	209.4
	Enl. F.	214.0	212.6	222.5
	Enl. G.	208.7	210.4	211.4
Trig.	Officer	111.9	127.4	129.0
	Enl. F.	129.8	126.4	128.4
	Enl. G.	118.6	114.5	121.1
Typical Sample Sizes	Officer	107	122	120
	Enl. F.	58	58	63
	Enl. G.	143	170	146

Table XIV-6

SUMMARY OF P VALUES FOR EXPOSURE INDEX ANALYSIS
OF NINE HEPATIC VARIABLES

VAR	OCC CAT	P Values for Models with Interaction: EXP CAT	ALC	IC	DC	aHb	EXP X ALC	EXP X IC	EXP X DC	EXP X anti HBsAg	P Values for Models With No Interaction: Exp Cat	ALC	IC	DC	anti HBsAg
SGOT	OFF	.563	<.001	-*	-	-	-	-	.009	-	.512	<.001	-	.047	-
	ENL.F.	.885	<.001	-	-	.037	-	-	-	-	.538	<.001	-	-	.035
	ENL.G.	.698	<.001	-	-	-	-	-	-	-	.409	<.001	-	-	-
SGPT	OFF	.463	<.001	-	-	-	-	.081	-	-	.812	<.001	-	-	-
	ENL.F.	.909	-	-	-	-	-	-	-	-	.411	-	-	-	-
	ENL.G.	.467	-	-	-	-	-	-	-	-	.862	-	-	-	-
GGPT	OFF	.052	<.001	-	-	-	.089	-	-	-	.696	<.001	-	.040	-
	ENL.F.	.427	<.001	-	-	-	.049	-	-	-	.224	<.001	-	-	-
	ENL.G.	.093	<.001	-	.010	-	-	-	-	-	.574	<.001	-	.020	-
ALK PHOS	OFF	.192	-	-	-	-	<.001	-	-	-	.280	-	-	-	-
	ENL.F.	.685	-	-	-	-	-	-	-	-	.855	-	-	-	-
	ENL.G.	.629	-	-	-	-	-	-	-	-	.710	-	-	-	-
TOT BILI	OFF.	.643	-	-	-	-	-	-	-	-	.885	-	-	-	-
	ENL.F.	.449	.029	-	-	-	-	-	-	.086	.560	.011	-	-	-
	ENL.G.	.606	-	-	.010	-	-	-	-	-	.642	-	.023	.008	-
DIR BILI	OFF	.992	-	-	-	-	-	-	-	-	.856	-	-	-	-
	ENL.F.	.399	-	-	-	-	-	-	.060	.006	.310	-	-	-	-
	ENL.G.	.823	-	-	-	-	-	-	-	-	.697	-	-	-	-
LDH	OFF	.516	-	-	-	-	-	-	-	-	.758	-	-	-	-
	ENL.F.	.656	.018	-	-	-	-	-	-	-	.174	.019	-	-	-
	ENL.G.	.300	-	.050	-	-	-	-	-	.049	.360	.034	.036	-	-
CHOL	OFF	.290	-	-	-	-	-	-	-	-	.602	-	-	-	-
	ENL.F.	.310	.031	-	-	-	-	-	-	-	.343	.037	-	-	-
	ENL.G.	.096	-	-	-	-	.026	-	.058	-	.841	-	-	-	-
TRIG	OFF.	.394	-	-	-	-	-	-	-	-	.244	-	-	-	-
	ENL.F.	.468	.045	.044	-	-	-	-	-	-	.980	-	-	-	-
	ENL.G.	.890	-	-	-	-	-	-	-	-	.768	-	-	-	-

* - Indicates P > 0.050 for main effects P > 0.100 for interactions.

Table XIV-7
EXPOSURE - COVARIATE INTERACTION EFFECTS FOR NINE HEPATIC VARIABLES

Var	Occ Cat	Interact	Level of Interact	Exposure Level	Slope	P Value on Test of Slope Against Null Hypothesis of Zero Slope
SGOT	Officers	Exp x DC	.009	Low	$-.201 \times 10^{-4}$ units/day	.286
				Med	$.021 \times 10^{-4}$ units/day	.924
				High	$.674 \times 10^{-4}$ units/day	.002
GGPT	Enlisted Flying	Exp x ALC	.049	Low	.0828 units/drk/day	<.001
				Med	.0561 units/drk/day	.002
				High	.0288 units/drk/day	.037
ALK PHOS	Officers	Exp x ALC	<.001	Low	-.0442 units/drk/day	<.001
				Med	.0131 units/drk/day	.254
				High	-.0015 units/drk/day	.864
DIR BILI	Enlisted Flying	Exp x Anti HB_sAg	.006	Low	.3713 mgm/dl	.013
				Med	-.2246 mgm/dl	.071
				High	.1752 mgm/ml	.134
LDH	Enlisted Ground	Exp x Anti Hb_sAg	.049	Low	.0329 units	.159
				Med	-.0407 units	.085
				High	-.0330 units	.128
CHOL	Enlisted Ground	Exp x ALC	.026	Low	.0039 mgm/dl/drk/day	.284
				Med	-.0065 mgm/dl/drk/day	.043
				High	.0054 mgm/dl/drk/day	.147

Alcohol use is associated with increasing GGPT levels among enlisted flying personnel, but the increase in GGPT falls smoothly with increasing exposure levels. On the other hand, alcohol use is associated with decreasing alkaline phosphatase levels among Ranch Hand officers in the low exposure group.

There are 2 interactions between exposure group and antibody to Hepatitis B antigen. Direct bilirubin levels are higher in enlisted flying personnel who are antibody positive and are in the low or high exposure groups. Direct bilirubin levels are lower in individuals who are antibody positive but in the medium exposure group. LDH is higher among enlisted ground Ranch Handers who are antibody positive and are in the low herbicide exposure group while LDH levels are lower among antibody positive individuals in the medium and high exposure groups.

An exposure-by-alcohol use interaction effect on cholesterol levels shows positive slopes in the low and high exposure categories but a negative slope in the medium exposure category.

Thus, of the 6 statistically significant interactions noted in this exposure index analysis only 1, the SGOT-degreasing chemical interaction, supports an interpretation of herbicide effect. But this interpretation is markedly weakened by the presence of the 5 uninterpretable patterns.

3. Urinalysis Determinations Related to Porphyrin Metabolism

Three components associated with porphyrin metabolism were determined and are analyzed here: uroporphyrin, coproporphyrin and d-aminolevulinic acid. Data addressing these 3 variables were analyzed looking for differences between the Ranch Hand and comparison groups and looking for associations with indexed herbicide exposure within the Ranch Hand group.

In examining the uroporphyrin, coproporphyrin and d-aminolevulinic acid data for Ranch Hand - comparison group differences, adjustments were accomplished for the following 6 variables: current alcohol use in drinks per day (ALC), blood urinary nitrogen (BUN), creatinine clearance (CCL), days of exposure to industrial chemicals (IC), days of exposure to degreasing chemicals (DC) and presence or absence of antibody to hepatitis B antigen. Adjustments were accomplished treating the dependent variable and all independent variables except antibody to hepatitis B antigen as continuous variables in a generalized linear model analysis. Since the compounds uroporphyrin, coproporphyrin and d-aminolevulinic acid are all measured in 24-hour urine collections, only data from subjects who complied with the full collection of urine are used in the analysis (620 Ranch Handers and 439 comparisons). Also, febrile participants and individuals with HB_sAg have been removed. In the adjusted analyses the dependent variable was normalized by using a logarithmic (base 10) transformation.

Table XIV-8 provides uroporphyrin, coproporphyrin and d-aminolevulinic acid unadjusted means, adjusted means and percent abnormality. For uroporphyrin, values greater than 60 were considered abnormal, for coproporphyrin, values greater than 235 and for d-aminolevulinic acid, values greater than 7000 were counted as abnormal.

Table XIV-8

UNADJUSTED MEANS, ADJUSTED MEANS AND PERCENT ABNORMALITY FOR THREE COMPOUNDS RELATED TO PORPHYRIN METABOLISM

		Unadjusted Means	Adjusted Means	% Abnormal
Uroporphyrin	RH	30.5	*	6.5%
	COM	30.8	*	6.8%
Coproporphyrin	RH	31.2	*	0.2%
	COM	30.8	*	0.0%
d-aminolevulinic acid	RH	2328.9	2337.1	0.0%
	COM	2383.2	2371.4	0.0%

* adjusted means not represented due to interaction

Table XIV-9

SUMMARY OF RESULTS UNMATCHED ANALYSES OF THREE COMPOUNDS RELATED TO PORPHYRIN METABOLISM P-VALUES FOR MODELS WITH INTERACTION

VAR	Gp	ALC	BUN	CCL	IC	DC	Anti HBsAg	Gp x ALC	Gp x BUN	Gp x CCL	Gp x IC	Gp x DC	Gp x Anti HBsAg
URO	.227	-	<.001	<.001	-	-	-	-	.077	-	-	-	-
COPRO	.490	-	<.001	<.001	-	.049	-	.045	.097	-	-	-	-
ALA	.145	-	-	<.001	-	-	.014	-	-	-	-	-	-

Table XIV-9 displays the detailed analyses. No overall group differences are observed. With uroporphyrin a borderline significant group-by-BUN interaction (P = 0.077) was observed. In the Ranch Hand group, the uroporphyrin-BUN slope was -0.010 uroporphyrin logarithm units per BUN unit, while the comparison slope was steeper (-0.017). A borderline group-by-BUN interaction was also noted in the coproporphyrin data. In the Ranch Hand group, the coproporphyrin-BUN slope was -0.014 coproporphyrin logarithmic units per BUN unit, while the comparison slope was again steeper (-0.023). Lastly, a group-by-alcohol interaction was detected in the coproporphyrin data (P = 0.045). The Ranch Hand slope was positive (+0.013) while the comparison slope was negative (-0.008).

Table XIV-10

SUMMARY OF P VALUES FOR EXPOSURE INDEX ANALYSES OF THREE COMPOUNDS
RELATED TO PORPHYRIN METABOLISM

VAR	OCC CAT	EXP CAT	ALC	BUN	CCL	IC	DC	aHb	EXP x ALC	EXP x BUN	EXP x CCL	EXP x IC	EXP x DC	Exp x Anti HB_sAg
URO	OFF	.207	-	-	<.001	-	-	-	-	-	-	-	.033	-
	ENL F.	.670	-	-	-	-	-	-	-	-	-	-	-	-
	ENL G.	.882	-	.010	.050	-	-	-	-	-	-	-	-	-
COPRO	OFF	.630	-	-	.022	.035	-	-	-	-	-	-	-	-
	ENL F.	.498	-	<.001	-	-	-	-	-	-	-	-	-	-
	ENL G.	.699	-	.016	.015	-	-	-	-	-	-	.016	-	-
ALA	OFF	.279	-	-	<.001	-	-	-	-	-	-	-	-	-
	ENL F.	.135	-	-	<.001	-	-	-	.028	-	-	-	-	-
	ENL G.	.312	-	-	<.001	.020	-	-	-	-	-	.040	.042	-

Table XIV-11

TABLE OF UNADJUSTED MEANS FOR THREE COMPOUNDS
RELATED TO PORPHYRIN METABOLISM

Variable	Occupational Category	N	Low Exposure	Medium Exposure	High Exposure
Uroporphyrin	Officers	212	28.9	26.9	31.3
	Enlisted Fly.	106	38.7	27.8	31.6
	Enlisted Gnd.	282	31.1	32.4	29.8
Coproporphyrin	Officers	212	32.4	26.7	29.9
	Enlisted Fly.	106	36.4	31.1	32.5
	Enlisted Gnd.	282	31.6	30.9	32.8
d-amino	Officers	212	2221	2312	2211
levulinic	Enlisted Fly.	106	2460	2510	2381
Acid	Enlisted Gnd.	282	2290	2441	2271

Table XIV-12

EXPOSURE-COVARIATE INTERACTIONS FOR THREE COMPOUNDS RELATED TO PORPHYRIN METABOLISM

Variable	Occupational Category	Interaction	P Value for Interaction	Exposure Level	Slope
Uropophyrin	Officer	Exp x DC	.033	Low	-.000043
				Med	.000074
				High	.000190
Copro-porphyrin	Enlisted Ground	Exp x IC	.016	Low	$.301 \times 10^{-4}$
				Med	$-.540 \times 10^{-4}$
				High	$.176 \times 10^{-4}$
d-amino levulinic acid	Enlisted Flying	Exp x ALC	.028	Low	.00045
				Med	-.02922
				High	.01445
d-amino levulinic acid	Enlisted Ground	Exp x IC	.040	Low	$-.1450 \times 10^{-4}$
				Med	$-.2944 \times 10^{-4}$
				High	$.0315 \times 10^{-4}$
d-amino levulinic acid	Enlisted Ground	Exp x DC	.042	Low	$-.0538 \times 10^{-4}$
				Med	$.0398 \times 10^{-4}$
				High	$.0394 \times 10^{-4}$

The literature indicates elevated porphyrin compound excretion resulting from sufficient dioxin exposure. The pattern found here is one of higher Ranch Hand uroporphyrin or coproporphyrin levels relative to comparisons when there are concomitantly higher BUN levels, or, in the case of coproprophyrin, when there is higher alcohol ingestion. No overall group differences are observed.

Tables XIV-10, XIV-11 and XIV-12 display the results of exposure index analyses within the Ranch Hand group. Starting with Table XIV-10, no statistically significant overall group differences are seen and 5 statistically significant($P \leq 0.050$) group-covariate interactions are noted. Table XIV-11 displays unadjusted group means for the porphyrin metabolism related variables and, as indicated by the statistical testing of overall group differences, no trends with exposure index are observed.

The 5 exposure-by-covariate interactions are listed in Table XIV-12; however, only the exposure index by degreasing chemical interactions follow a classical dose-response pattern. Specifically, Ranch Hand officers with greater herbicide exposure, as measured by the exposure index, have greater increases in uroporphyrin output in response to degreasing chemical exposures than do Ranch Hand officers with less herbicide exposure. The same pattern is seen in the enlisted ground d-aminolevulinic acid data.

4. Clinical Variables

Sixteen of 1027 Ranch Handers (1.56%) were diagnosed as having hepatomegaly while 6 of 769 comparisons (0.78%) had that finding ($P = 0.138$) with an approximate 70% power. In the Ranch Hand group, the cases of hepatomegaly appear to be randomly distributed within the 3 exposure categories; however, due to the small number of cases statistical testing is not powerful. These data on hepatomegaly are shown in Table XIV-13 (febrile participants and individuals with HBsAg have been removed).

Table XIV-13

CASES OF HEPATOMEGALY IN THE RANCH HAND COHORT BY OCCUPATION AND EXPOSURE CATEGORY

	Exposure Index					
	Low		Medium		High	
Occupational Category	Cases	N	Cases	N	Cases	N
Officers	2	110	2	124	2	123
Enlisted Flying	1	59	2	58	2	63
Enlisted Ground	0	148	3	176	1	147

Eighteen of 1027 Ranch Handers (1.75%) reported an enlarged liver during response to questionnaire inquiry while 13 of 760 comparisons (1.71%) reported the same.

The study questionnaire also inquired about a medical history of hepatitis, jaundice, cirrhosis, and a general category called other liver conditions. Ranch Hand and comparison responses to these questions are shown in Table XIV-14. Ranch Hand respondents differ from comparisons only in the other liver category. Thirteen of the 16 Ranch Handers reporting other liver conditions have had their report verified by medical record. One comparison has had his condition verified. A display of the verified findings is shown in Table XIV-15 (febrile individuals and HBsAg positive individuals were left in the analysis).

Table XIV-14

SPECIFIC LIVER DISORDERS REPORTED ON QUESTIONNAIRE

Reported Event	Ranch Hand		Comparison		P Value
	Yes	No	Yes	No	
Hepatitis	40	1005	32	741	>0.50
Jaundice	44	1001	35	738	>0.50
Cirrhosis	4	1041	3	770	>0.50
Other	16	1029	2	771	0.004

Table XIV-15

OTHER LIVER CONDITIONS REPORTED BY STUDY PARTICIPANTS AND VERIFIED BY MEDICAL RECORDS

	ICD Code	Code Meaning	Number
Ranch Hand:			
	2724	Hyperlipidemia	1
	570	Liver necrosis	1
	5739	Unspecified	10
	7904	Enzyme elevation	1
Comparison:	5719	Chronic unspecified	1

Table XIV-16

REPORTED SKIN PATCHES, BRUISES OR SENSITIVITY
IN RANCH HAND PARTICIPANTS BY
OCCUPATION AND EXPOSURE CATEGORY

Occupational Category	Exposure Index: Low			Medium			High		
	Cases	%	N	Cases	%	N	Cases	%	N
Officers	36	32.4	111	48	37.5	128	44	35.2	125
Enlisted Flying	27	45.8	59	28	47.5	59	37	56.1	66
Enlisted Ground	74	49.0	151	82	45.8	179	76	51.4	148

Seeking historical evidence of porphyric symptoms, questions concerning skin changes that could have been associated with porphyria cutanea tarda were asked (specifically, skin patches, bruisibility or sensitivity). Of 1045 Ranch Hand respondents, 462 or 44.2% reported these skin symptoms while 278 of 773 comparisons or 36.0% reported these conditions. These reported cases indicate a statistically significant group difference ($P < 0.001$); however, no regression with exposure index was noted (data given in Table XIV-16).

The historical and hepatomegaly data support an interpretation of some group difference. However, no positive association with herbicide exposure has been noted.

5. Summary and Conclusion

Ranch Handers have slightly greater GGPT and LDH levels than the comparisons while having lower cholesterol levels. Also, Ranch Hand SGOT, SGPT and LDH levels are more highly correlated to (and therefore may be more influenced by) materials with an hepatic effect, namely, alcohol, degreasing compounds and industrial chemicals. No group differences were noted in alkaline phosphatase or bilirubin levels.

Borderline statistically significant group differences have been detected in uroporphyrin and coproporphyrin levels in association with BUN, and in coproporphyrin levels in association with alcohol ingestion. No overall group differences were detected in these compounds or delta aminolevulinic acid values.

Twice as many Ranch Handers as comparisons had enlarged livers on physical examination, but this difference was not statistically significant. Statistically significant group differences were noted in the occurrence of miscellaneous liver disorders exclusive of hepatitis, jaundice and cirrhosis, verified by medical record review. Ranch Handers self reported 23% more skin changes of the type associated with porphyria cutanea tarda than did the comparison participants, and the group difference was statistically significant. Clinically apparent porphyria was not evident at physical examination.

The observed group differences in liver-related biochemical variables found in the blood, and in porphyrin metabolism compounds found in the urine are most likely of minor or negligible medical importance at the present time. The verified reports of liver morbidity are of greater clinical interest.

The exposure index analyses do not support an interpretation of herbicide effect with respect to any of the group differences summarized.

Chapter XV

DERMATOLOGIC EVALUATION

A thorough dermatologic assessment was deemed essential because chloracne is the only recognized definitive clinical end point following exposure to chlorophenols and dioxin. Over one-half of all veteran complaints recorded in the Veterans Administration Herbicide Registry cited dermatologic symptoms. These facts, coupled with the knowledge that chloracne is transient following a single point exposure (Homberger, 1979), suggested that there is a significant potential to misclassify adolescent acne and chloracne. While the issue of correct diagnosis could be resolved by biopsies and histopathologic characterizations in all participants, this approach was rejected on ethical grounds, as well as concern for the adverse impact of biopsy procedures on future study participation. Consequently, the dermatologic assessment was carefully planned to collect historical and distributional dermatologic data by questionnaire, followed by a detailed corroborative physical examination, supplemented by voluntary biopsies when indicated. Most data reported in this chapter are from the 1045 Ranch Handers and the 773 originally selected comparison individuals enrolled in the study. Minor fluctuations from these denominators reflect missing dependent variable or covariate data. Relative risks and confidence intervals are shown for all dependent variables in Appendix XVIII.

1. Questionnaire Data

The in-home study questionnaire collected detailed medical histories on the occurrence of acne. These data are displayed in Table XV-1 and show that the Ranch Handers reported slightly more acne than their comparisons.

Table XV-1

REPORTED OCCURRENCE OF ACNE BY GROUP

Group	No Acne		Reported Acne		Total	
	Number	Percent	Number	Percent	Number	Percent
Ranch Hand	659	63.3	382	36.7	1041	100
Comparison	498	64.8	271	35.2	769	100

Reported acne group contrast: P = 0.52

Beginning and end dates of up to three sustained periods of acne activity re recorded for each individual on the questionnaire. Since only acne after 61 could be possibly induced by herbicide exposure, cases of post-1961 acne re placed in time reference to each individual's RVN tour(s). This temporal stribution was not statistically different with respect to group membership. ese data are reflected in Table XV-2.

Table XV-2

REPORTED POST-1961 ACNE BY TIME OF THE SOUTHEAST ASIA [SEA] TOUR(S) BY GROUP

	Pre-SEA Only		Post-SEA Only		Pre- and Post-SEA*	
roup	Number	Percent	Number	Percent	Number	Percent
nch Hand = 179	62	34.6	31	17.3	86	48.0
mparison = 116	51	44.0	17	14.7	48	41.4

ported acne by group by pre/post SEA: P = 0.27
ported acne (Post SEA) relative risk: 1.18, 95% Conf. int. (.67, 2.18)

*Such acne could have been separate cases or the same case starting before his RVN tour and ending afterwards.

Durations of the cumulative acne episodes were distributed by 5-year itervals and contrasted by group and SEA category. These data are shown in ible XV-3.

Table XV-3

DURATION OF ACNE IN 5-YEAR CATEGORIES BY SEA TOUR AND GROUP MEMBERSHIP

	Duration in Years				
Pre-SEA ONLY	≤5	5 <Yr ≤10	10 <Yr ≤15	15 <Yr ≤20	Total
Ranch Hand	44	15	2	1	62
Comparison	38	12	0	1	51
			P = 0.63		
Post-SEA ONLY					
Ranch Hander	15	4	11	1	31
Comparison	9	2	4	2	17
			P = 0.61		

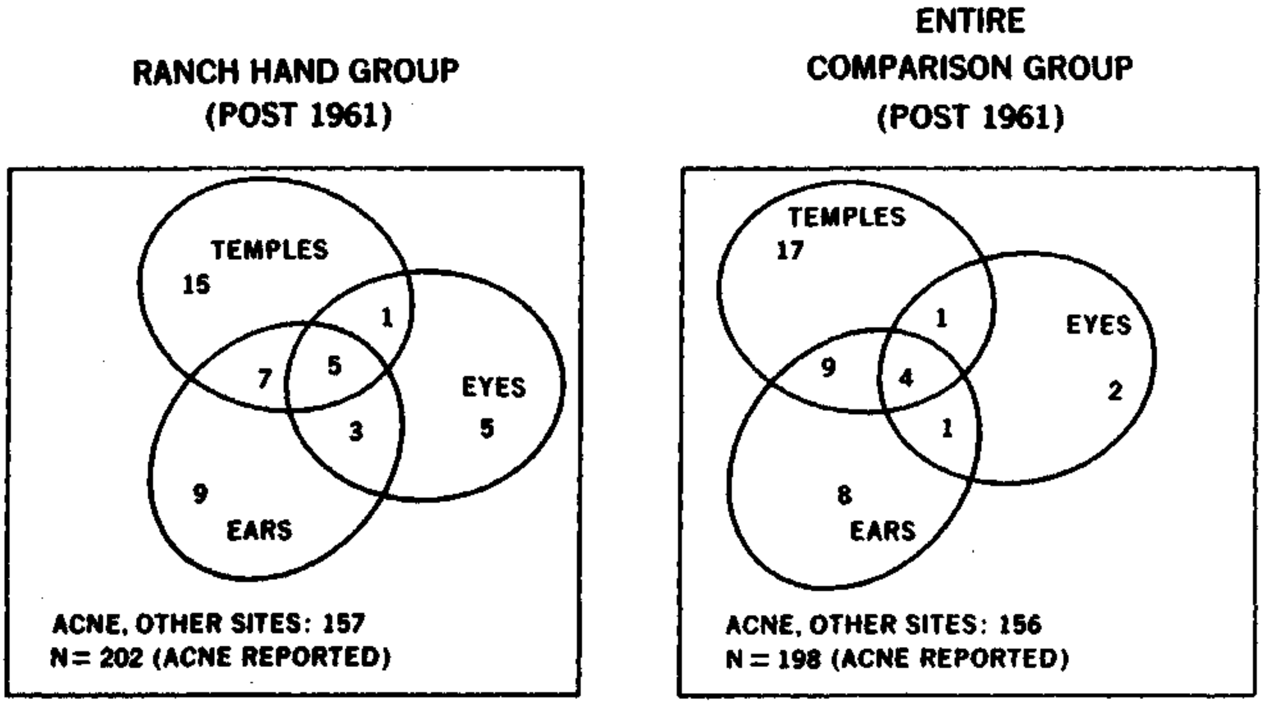
Thus, these SEA tour categories suggested that there were no group differences for the pre-SEA or post-SEA acne. Questionnaire information on whether the participant consulted a physician for his acne was used as an indirect measure of the clinical severity of the acne. Of 70 Ranch Handers with acne post-1961 who were asked this question, 29 (41.4%) responded as having visited a physician as contrasted to 15 of the 45 (33.3%) comparisons (P = 0.38), suggesting that there was not a statistically significant difference in the clinical severity of their acne.

Since chloracne, following mild to moderate exposures, is classically found in skin areas on the temples, eyes/eyelids, and ears (eyeglass distribution), questions on rash locations and combinations of locations were presented to each participant reporting acne. Of the 117 post-SEA plus pre- and post-SEA cases of acne in Ranch Handers after SEA duty, 75 (64%) reported no acne at any of these locations, while 36 (55%) of the 65 post-SEA plus pre- and post-SEA comparisons reported none. These proportions are not significantly different (P = 0.25), and the occurrence of skin disease which could potentially be chloracne does not differ in the two groups. There were only four individuals, two in each group, with acne confined exclusively to the classical chloracne areas.

As further corroboration of these anatomically categorized data, a Venn diagram was constructed for post-1961 acne lesions on the temples, ears, and eyes for the Ranch Hand group and the entire comparison group. These data are shown in Figure XV-I and display remarkable visual concordance.

Figure XV-1

VENN DIAGRAM OF POST-1961 TEMPLE, EAR, AND EYE ACNE BY GROUP



2. <u>Physical Examination Data</u>

All physical examination data were described using a diagnostic checklist, and abnormalities were annotated on a full body diagram. Color photographs were obtained at the dermatologist's discretion, and 14 lesions were biopsied. Of the 14 biopsies collected from 11 patients, none were suggestive of chloracne. No cases of chloracne were diagnosed. Histologic descriptions of these biopsies are presented in Table XV-4.

Table XV-4

BIOPSY RESULTS

Number	Histologic Description
3	Active degeneration
2	Inclusion cysts
2	Epidermal cysts
1	Basal cell carcinoma
1	Intradermal melanosis
1	Seborrheic keratosis
1	Pigmented nevus
1	Psoriasiform dermatitis
1	Chronic inflammation
1	Insect bite

The five most common diagnoses and the P value for group differences are shown in Table XV-5. Abnormal skin findings were prevalent but almost identical in both groups (i.e., 45.0% in Ranch Handers, and 44.9% in the comparisons; P = 0.97). Only for the miscellaneous diagnoses of "Other Abnormalities" (which included 15 diagnostic categories) was there a statistically significant group difference, with the comparisons having more disease than the Ranch Handers.

Table XV-5

PREVALENCE OF DERMATOLOGIC DIAGNOSES IN PERCENT

Diagnoses	Ranch Hand N = 1045	Comparison N = 773	P Value	Relative Risk	95% Conf int
Comedones	21.7	20.7	0.60	1.05	(.87,1.26)
Acneiform lesions	18.3	17.5	0.66	1.05	(.85,1.29)
Acneiform scars	11.2	10.4	0.57	1.08	(.82,1.43)
Cysts	11.6	10.5	0.46	1.10	(.84,1.46)
Hyperpigmentation	8.3	7.1	0.35	1.17	(.84,1.65)
Other abnormalities	12.6	16.3	0.03	.77	(.81, .98)
Any abnormality	45.0	44.9	0.97	1.00	(.90,1.11)

Based upon the four most prevalent diagnoses in Table XV-5 (comedones, acneiform lesions, acneiform scars, and dermal cysts), all of which should encompass the diagnostic possibility of chloracne, a dermatologic index was constructed for each study participant. A score of zero was given if none of the four lesions were noted, and a score of 1 was assigned if one lesion was diagnosed, etc. These data are displayed in Table XV-6.

Table XV-6

DERMATOLOGIC INDEX SCORE BY GROUP

Group	Scores 0 Number	0 %	1 Number	1 %	2 Number	2 %	3 Number	3 %	4 Number	4 %
Ranch Hand (N = 1045)	633	60.6	234	22.4	124	11.9	42	4.0	12	1.1
Comparison (N = 773)	487	63.0	157	20.3	95	12.3	27	3.5	7	0.9

P = 0.74

The distributions of these scores did not differ significantly, suggesting a similar crude clinical severity between the groups.

3. Questionnaire - Examination Correlations

The dermatologic index was contrasted to the historical occurrence of acne by group. These data are shown in Table XV-7.

Table XV-7

DERMATOLOGIC INDEX IN PERCENT BY QUESTIONNAIRE HISTORY OF ACNE BY GROUP

History	Group	Score 0	1	2	3	4	P Value
No Acne	Ranch Hand	66.3	21.4	9.4	2.4	0.5	0.72
	Comparison	69.1	18.1	9.6	2.6	0.6	
Acne ≤1961	Ranch Hand	55.3	25.1	13.4	4.5	1.7	0.84
	Comparison	55.1	21.8	17.7	4.1	1.4	
Acne >1961	Ranch Hand	47.3	23.2	17.7	8.9	3.0	0.82
	Comparison	48.4	26.6	16.9	6.4	1.6	

These data show that the dermatologic index does not differ significantly by group for any historical subset. And, as can be observed in Table XV-7, there is a positive association between the history (and time) of acne and the dermatologic index, regardless of group membership. An additional analysis of the dermatologic index for each individual who reported acne after his SEA tour (post-SEA only) did not reveal significant Ranch Hand-comparison differences ($P = 0.50$).

4. Exposure Index Analyses

Several comparisons were made using the exposure index and both historical and examination findings in the Ranch Hand group. Two historical parameters (incidence of acne and severity of acne) and the dermatologic examination findings were contrasted to the exposure index after stratifying for occupational categories by log-linear models. The historical-exposure analyses were essentially negative. Major dermatologic lesions from the examination were contrasted to the exposure index by occupational category. This analysis is presented in Table XV-8.

Table XV-8

PERCENTAGE OF SPECIFIC SKIN LESIONS IN RANCH HANDERS
BY EXPOSURE LEVEL BY OCCUPATIONAL CATEGORY
(POST 1961 DATA ONLY)

Condition	Occupational Group	Exposure Level Low %	Medium %	High %	P Value
All skin abnormalities	Officers	57.1	22.2	21.4	0.20
	Enlisted Flying	14.3	16.7	60.0	0.17
	Enlisted Ground	39.5	35.8	25.0	0.40
Comedones	Officers	14.3	22.2	21.4	0.91
	Enlisted Flying	57.1	50.0	20.0	0.42
	Enlisted Ground	18.6	24.5	31.2	0.45
Acneiform Lesions	Officers	0	33.3	50.0	0.08
	Enlisted Flying	57.1	16.7	20.0	0.23
	Enlisted Ground	37.2	22.6	37.5	0.21
Acneiform Scars	Officers	28.6	11.1	21.4	0.68
	Enlisted Flying	71.4	50.0	40.0	0.53
	Enlisted Ground	10.9	28.3	31.2	0.57
Inclusion Cysts	Officers	14.3	0	14.3	0.49
	Enlisted Flying	14.3	50.0	20.0	0.32
	Enlisted Ground	18.6	18.6	27.1	0.53
Hyperpigmentation	Officers	0	11.1	7.1	0.72
	Enlisted Flying	14.3	16.7	0	0.64
	Enlisted Ground	9.3	15.1	3.1	0.20

Thus, of the 18 exposure analyses, none were statistically significant (although based upon small sample sizes). Similarly, the relationship between the dermatologic index and exposure index was explored. For all three occupational categories, the dermatologic index showed no significant correlation to the exposure index, as reflected in Table XV-9.

Table XV-9

RANCH HAND DERMATOLOGIC INDEX IN ALL OCCUPATIONAL CATEGORIES
BY THE EXPOSURE INDEX
(POST 1961 DATA ONLY)

	Dermatologic Index			
	0		≥ 1	
Exposure Level	Number	Percent	Number	Percent
Low	26	45.6	31	54.4
Medium	28	41.2	40	58.8
High	20	39.2	31	60.8

$P = 0.78$

5. Summary

A comprehensive dermatologic assessment was conducted by questionnaire and physical examination. The questionnaire data revealed that the incidence of past acne, its time of occurrence relative to the individual's SEA tour(s), its severity and duration, and its anatomic location did not significantly differ between the Ranch Hand and comparison groups. No cases of chloracne were diagnosed at physical examination or by biopsy. No group differences were noted for the five most prevalent dermatologic diagnoses. The category, other abnormalities (containing 15 dermatologic conditions), was significantly larger for the comparison group than for the Ranch Hand group. However, when all skin abnormalities were considered, the group rates were essentially identical. A dermatologic index was constructed to account for the number of skin abnormalities per individual (severity index) that might encompass a diagnosis of chloracne. The index was not associated with group membership but showed some correlation with a total history of past acne in both groups. There were no associations between historical or dermatological examination findings and exposure level in any occupational category of the Ranch Hand group.

Chapter XVI-1

CARDIOVASCULAR EVALUATION

1. Introduction

The effects of Herbicide Orange and its dioxin contaminant on the cardiovascular system are not well defined. Both bradycardia and tachycardia have been suggested in acute heavy exposures to the 2,4-D and 2,4,5-T components, but the cardiovascular effects following chronic low dose exposure are essentially unknown. The thrust of this cardiovascular evaluation has been to collect important data by questionnaire, physical examination, and laboratory testing, that would identify Ranch Hand-comparison group differences after accounting for the effects of confounding variables. Of the well-established risk factors for cardiovascular disease, smoking, cholesterol level or cholesterol to high density lipoprotein (HDL) ratio, and age were selected as covariates in most analyses (Brand et al, 1976). The covariates were categorized as follows: age, ≤40, 40 years 1 month - 59 years 11 months (abbreviated 40 < > 60), and 60 years or more; smoking, 0 pack-years, 1-10 pack-years, and 11 or more pack-years; cholesterol, ≤180 mg/dl, 181-279 mg/dl, and ≥280 mg/dl; and cholesterol-HDL ratio, <5.3, ≥5.3. In complex analyses with sparse data, trichotomous covariates were reduced to dichotomous ones. The cutpoint for cholesterol-HDL ratio was derived from data on rated Air Force personnel referred for cardiovascular diagnostic examination; it is an unweighted average of means of flyers verified at cardiac catheterization as having or not having occlusive coronary atherosclerosis. A more optimal approach, based upon a median HDL value of the comparison group, will be used in subsequent reports. Statistically significant interactions between these covariates were not explored in detail when there was no effect on group membership and when the interactions were consonant with the classical epidemiology of cardiovascular disease. Analyses of weak risk factors in the data will be presented in subsequent reports. Because of the low proportion of Black participants in both groups, covariate adjustment by race was not possible. Consequently, a variety of dependent variable analyses by race, unadjusted for age, smoking, and cholesterol, are discussed throughout this chapter. In addition, where adjusted group differences were found to be statistically significant, other covariates (e.g., percent body fat, current smoking, history of intermittent claudication, testosterone level, differential cortisol level, etc.) have been used to reanalyze all data in an attempt to clarify the clinical significance of the finding.

Most analyses herein are based upon Ranch Hand contrasts to the "originals" of the comparison group. Where group associations are statistically significant or of general interest, other comparison group denominators have been used (e.g., matched originals only and the entire comparison group). Further, for specific analyses, participants with diabetes and pedal edema have been deleted. Small denominator fluctuations are also inherent in these analyses because of missing covariate or dependent variable information. Thus, tabular data may not be directly comparable between analyses because of the type of covariate adjustment, or the denominator of the comparison group, or the deletion of certain medical conditions thought to confound a specific clinical diagnosis. In general, covariates having a nonsignificant association with the dependent variable were removed from the analysis. The statistical analyses are based on log-linear models (BMDP-4F), logistic regression (BMDP-LR), and generalized linear models, chi-square, t tests, and matched covariate analyses (Breslow, 1982). Relative risks and confidence intervals, computed using the hypergeometric distribution (Thomas, 1971) and the normal approximation (Fleiss, 1981), are shown for all dependent variables in Appendix XVIII.

2. Central Cardiovascular System

a. Systolic Blood Pressure

Abnormal systolic blood pressure was defined as pressure in excess of 140 mmHg by standard observer auscultation. All blood pressures were obtained in a sitting position. Second or third readings were recorded on those individuals who manifested an initial elevation. There was no significant difference in systolic blood pressure (P = 0.248) between the non-Black Ranch Hand and the non-Black original comparison group after adjusting for age, smoking, and cholesterol level. These data are reflected in Tables XVI-1-1 and XVI-1-2. Diabetics (2-hour postprandial glucose ≥120 mg/dl) were removed from the analyses.

Table XVI-1-1

SYSTOLIC BLOOD PRESSURE
RANCH HANDERS AND THE ORIGINAL COMPARISONS VERSUS AGE
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	36	10.4	309	32	14.3	192	68	11.9	501
≥40	113	23.1	377	94	24.6	288	207	23.7	665

Systolic pressure between groups: P = 0.248
Relative risk under 40: .73,95% Conf int (.46,1.18)
Relative risk over 40: .94, 95% Conf int (.73,1.20)

Age versus systolic pressure (unadjusted for smoking and cholesterol): P <0.0001

The unadjusted systolic blood pressure by smoking history association, presented in Table XVI-1-2, is not significant (P=0.179) in these data.

Table XVI-1-2

SYSTOLIC BLOOD PRESSURE PARTICIPANTS BY SMOKING HISTORY (NON-BLACKS ONLY)

Smoking History in Pack-Years	Abnormal	% Abnormal	Normal
0	70	17.8	324
1-10	44	16.1	230
>10	161	20.8	612

P = 0.179

Ranch Handers and original comparisons reflected in these tables were also compared on systolic blood pressure as a continuous variable with adjustment for age, smoking history, HDL ratio, and body fat, via a general linear model. There was no significant difference between the groups on systolic blood pressure (P = 0.976). The Ranch Hand and original comparison adjusted means were 133.12 and 133.15, respectively. The covariates of age and body fat were both significantly associated with systolic blood pressure (P = 0.0001).

Additional categorical analyses comparing Non-Black Ranch Handers with the total non-Black comparison group adjusted for age, smoking, and cholesterol showed comparable nonsignificant intergroup differences (P = 0.366) for systolic blood pressure. The effects of age and smoking were statistically significant, P <0.0001 and P = 0.04, respectively. In addition, a chi-square analysis of Black Ranch Handers and Black individuals from the entire comparison group (diabetics removed) showed no group difference (P = 0.265) in systolic pressure.

b. Diastolic Blood Pressure

Diastolic blood pressure in excess of 90 mmHg was categorized as abnormal. No significant intergroup difference was noted after adjustment for age, smoking, and cholesterol level. These data are based upon non-Black, nondiabetic denominators and are presented in Table XVI-1-3.

Table XVI-1-3

DIASTOLIC BLOOD PRESSURE
IN RANCH HANDERS AND THE ORIGINAL COMPARISONS VERSUS AGE
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	18	5.2	327	12	5.4	212	30	5.3	539
≥40	57	11.6	433	53	13.9	329	110	12.6	762

Diastolic blood pressure between groups: P = 0.351
Relative risk under 40: .97,95% Conf. int. (.45,2.18)
Relative risk over 40: .84,95% Conf. int. (.58,1.21)

Age versus diastolic pressure (unadjusted for smoking and cholesterol): P <0.0001

The Ranch Handers and original comparisons (as represented in Table XVI-1-3) diastolic blood pressure was also compared as a continuous variable with adjustment for age, smoking history, HDL ratio, and body fat, via a general linear model. There was a borderline significant diastolic blood pressure by group by age interaction (P = 0.0585), indicating a change in the blood pressure by group association with level of age (<40, ≥40). However, separate analyses at each level of age revealed no significant group differences. In the under-40 age group, the diastolic blood pressure by group association was not significant (P = 0.435); the adjusted group means were 78.2 and 77.02 for Ranch Handers and comparisons, respectively. In the 40-and-over age group, the diastolic blood pressure by group association was not significant (P = 0.904); the Ranch Hand and comparison adjusted means were 80.7 and 81.7, respectively.

An intergroup log linear analysis of diastolic blood pressure for Blacks and non-Blacks using original comparisons showed comparable nonsignificant results (P = 0.573). Age was a significant covariate (P <0.0001) while the history of past smoking was not. An unadjusted contrast of Black Ranch Handers and Black individuals from the entire comparison group also showed similar nonsignificant group differences (P = 0.533).

c. Electrocardiograms (ECG's)

ECG's were obtained on all participants, following a minimum fast of 4 hours and abstinence from tobacco for 4 hours. The vast majority of ECG's were obtained by 1 or 2 technicians on dedicated and calibrated machines. The tracings were read by a contract clinic cardiologist and categorized into normal and abnormal groups, the latter consisting of right bundle branch block, left bundle branch block, nonspecific T wave changes, bradycardia, tachycardia, and other diagnoses. Grave findings were immediately discussed with the participant's family physician and appropriate follow-up was arranged. As shown in Table XVI-1-4, abnormal ECG findings were not associated with group membership (P = 0.987). For both the non-Black Ranch Hand and original comparison groups, there was a highly statistically significant (P <0.0006) association between abnormal ECG's and increased age.

Table XVI-1-4

ECG FINDINGS IN RANCH HANDERS AND THE ORIGINAL COMPARISONS
BY AGE, ADJUSTED FOR SMOKING HISTORY AND HDL RATIO
(NON-BLACKS ONLY)

	Ranch Hand			Original Comparisons			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	69	20.1	274	51	23.1	170	120	21.3	444
≥40	148	30.2	342	107	28.4	269	255	29.4	611

Abnormal ECG findings between groups: P = 0.987
Relative risk under 40: .87,95% Conf. int. (.62,1.23)
Relative risk over 40: 1.06,95% Conf. int. (.86,1.32)

ECG findings in both groups by age (unadjusted for smoking and HDL ratio): P = < 0.0006

When the ECG data in Table XVI-1-4 were redistributed into the categories of tachycardia, bradycardia, other abnormalities, and normal, an unadjusted analysis showed no significant differences between the Ranch Hand and original comparison group (P = 0.881).

An additional cardiac assessment was made on all past or present flying personnel in both groups. Participants' names and social security numbers were computer matched to the USAF ECG Repository, the world's largest ECG repository on flying personnel (Lancaster and Ord, 1972; Hiss and Lamb, 1962). Three hundred and fifty-four Ranch Handers and 282 original comparisons had between one and 10 previous tracings on file which had been diagnostically coded by stringent criteria. Accordingly, USAF cardiologists reviewed all 636 physical examination ECG's (without knowledge of group membership) and coded them by the standardized USAF criteria. The physical examination ECG was contrasted to the past ECG's and categorized as no change or degraded (no ECG's were improved in either group). These data analyzed by group membership and age are shown in Table XVI-1-5. Blacks and diabetics were removed from the analysis. This analysis is not adjusted for elapsed time between ECG readings.

Table XVI-1-5

CLINICAL COMPARISON OF CURRENT ECG'S TO PAST ECG'S IN FLYING PERSONNEL
BY GROUP MEMBERSHIP AND AGE
(NON-BLACKS ONLY)

	Ranch Hand			Comparison			Total		
	No Change	Degraded		No Change	Degraded		No Change	Degraded	
Age	Number	Number	Percent	Number	Number	Percent	Number	Number	Percent
<40	45	2	4.2	29	2	6.4	74	4	5.1
≥40	226	20	8.1	182	17	8.5	408	37	8.3
	271	22		211	19		482	41	

Because of sparse data in the under-40 age group, an analysis adjusted for both age and smoking was not possible; the unadjusted ECG change by group association was not significant (P = 0.652). In the 40-and-over age group, the ECG change by group association was not significant (P = 0.939), adjusted for smoking history. The smoking history covariate was borderline significant, P = 0.0852. In both the Ranch Hand and comparison groups combined, the age by ECG association (P = 0.412) was not significant. The unadjusted ECG change by smoking history association was significant (P = 0.018).

An overall analysis of systolic/diastolic blood pressures and ECG abnormalities was performed by group membership and adjusted for smoking (0, 1-10, >10 pack-years), cholesterol-HDL ratio (<5.3, ≥5.3), age (<40, ≥40) and differential cortisol level (continuous); Blacks and diabetics were omitted. The differential cortisol level is defined as the 7:30 AM cortisol measurement minus the 9:30 AM cortisol measurement. A logistic regression analysis showed similar nonsignificant results (as in Sections a-c above) that are presented in Table XVI-1-6.

Table XVI-1-6

RANCH HAND AND ORIGINAL COMPARISON GROUP CONTRAST FOLLOWING ADJUSTMENT
FOR AGE, SMOKING, CHOLESTEROL-HDL RATIO, AND DIFFERENTIAL CORTISOL RESULTS
(NON-BLACKS ONLY)

Dependent Variable	P Value
Systolic Blood Pressure	0.195
Diastolic Blood Pressure	0.351
ECG Abnormality	0.999

d. Heart Sounds

All valvular sound abnormalities were recorded following detailed auscultation. Fourth heart sounds were considered abnormal. If the participant indicated that the heart sound abnormality was a new finding, the diagnostician confirmed the abnormality. A review of the heart sound abnormalities in the non-Black Ranch Handers and original comparisons revealed that the data were too sparse for a fully adjusted analysis. An unadjusted group comparison was nonsignificant (P = 0.414), as was the unadjusted effect of age (P = 0.375). Similarly, an unadjusted analysis of Black Ranch Handers and comparison individuals did not demonstrate statistical significance (P = 0.799). A combined race and fully adjusted (age, smoking, cholesterol level) analysis of Ranch Handers and the entire comparison group is presented in Table XVI-1-7. These data also show no group differences (P = 0.592) but do reflect a significant association of heart sound abnormalities and increasing age (P <0.002).

Table XVI-1-7

HEART SOUND ABNORMALITIES
IN BLACK AND NON-BLACK RANCH HANDERS AND ALL COMPARISONS BY AGE

	Ranch Hand			Comparison			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
≤40	5	1.3	367	8	1.9	417	13	1.6	784
40<>60	11	2.3	476	15	2.7	542	26	2.5	1018
≥60	2	11.1	16	2	8.3	22	4	9.5	38

Abnormal heart sounds between groups: P = 0.592

Heart sound abnormalities in both groups by age: P < 0.002

3. Peripheral Cardiovascular System

The status of the peripheral cardiovascular system was evaluated by ophthalmoscopic examination of the eyegrounds for arterial-venous nicking and hemorrhages, auscultation of the carotid arteries, and bilateral palpation for the presence and quality of 5 peripheral pulses. The finding of a bilateral abnormality (e.g., bruits in both carotid arteries) was scored as 1 abnormality. Diminished or absent peripheral pulses were both designated as abnormal. While there is clearly recognized misclassification of the specific causes for the examination findings, it is judged to be of a minor nature; thus, the examination findings are deemed to be generally indicative of the presence or absence of severe arteriosclerosis. Abdominal x-rays to confirm the severity of the peripheral vessel arteriosclerosis were not obtained because of the possible impact of detected asymptomatic or clinically irrelevant kidney stones upon the flying status of active pilots.

a. Eyegrounds

Abnormal funduscopic findings were not associated with group membership (P = 0.965), but were highly correlated with increased age (P < 0.0001), as reflected in Table XVI-1-8. The additional covariates of smoking history and cholesterol-HDL ratio were nonsignificant in the analysis.

Table XVI-1-8

FUNDUSCOPIC ABNORMALITIES
IN RANCH HANDERS AND ORIGINAL COMPARISONS BY AGE
(NON-BLACKS ONLY)

	Ranch Hand			Comparison			Total Both Groups		
Age	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal	Abnormal	% Abnormal	Normal
<40	8	2.3	333	6	2.7	214	14	2.5	547
≥40	42	8.7	441	31	8.4	339	73	8.6	780

Funduscopic abnormalities between groups: P = 0.965
Relative risk under 40: .86,95% Conf. int. (.26,2.97)
Relative risk over 40: 1.04,95% Conf. int. (.65,1.67)

Funduscopic abnormalities in both groups by age (unadjusted for smoking and cholesterol-HDL ratio) P <0.0001

An unadjusted contrast of Black Ranch Handers and Black individuals from the entire comparison group showed similar nonsignificant results (P = 0.860).

b. Carotid Bruits

The prevalence of carotid bruits in both groups combined was 1.47%. Because of sparse data, an unadjusted analysis comparing non-Black Ranch Handers with non-Black original comparisons was performed; the group by carotid bruits association was nonsignificant (P = 0.269), as was the unadjusted age by carotid bruits association (P = 0.353). However, the larger analysis of both Black and non-Black Ranch Handers with the entire comparison group showed a group membership association of interest (P = 0.183) and a significant relationship between bruits and increasing age (P = 0.03).

c. Peripheral Pulses

The absence or diminished quality of 5 peripheral pulses was determined by detailed clinical palpation. One or more abnormal pulses were found in 12.8%(106/829) of the non-Black Ranch Handers as contrasted to 9.4% (56/596) in the non-Black original comparisons (P = 0.05) giving an unadjusted relative risk of 1.36 with a 95% confidence interval (.99, 1.88). The reader is referred to Appendix XVIII for complete relative risks and confidence intervals. Data on specific pulses are presented in Table XVI-1-9. The covariates of cholesterol-HDL ratio and percent body fat (<25%, ≥25%) were noncontributory in all of the analyses. Thus, the pulse variables were adjusted for age (<40, ≥40) and smoking (0, 1-10, >10 pack-years). Blacks, diabetics, and individuals with peripheral pitting edema were omitted from the analysis. Since most abnormalities were concentrated in the over 40 and > 10 pack-year group, these data were re-analyzed on that subset with the results shown in column three of Table XVI-1-9.

Table XVI-1-9

SUMMARY OF PERIPHERAL PULSE QUALITY:
RANCH HANDERS AND ORIGINAL COMPARISONS
(NON-BLACKS ONLY)

Pulse Examined, Number of Participants	Unadjusted P Value and Direction of Group Abnormalities	Unadjusted P Value for Age ≥40 Years and >10 Pack-Years	Unadjusted P Value Age Versus Pulse (Groups Combined)
Radial N = 1414	0.147 (RH > C)	Sparse Data	0.668
Femoral N = 1414	0.147 (RH > C)	0.117 (RH > C)	0.157
Popliteal N = 1414	0.0255 (RH > C)	0.0159 (RH > C)	0.0065
Dorsalis Pedis N = 1413	0.0644 (0.0406)* (RH > C)	0.0375 (RH > C)	0.0003
Posterior Tibial N = 1413	0.312 (0.250)* (RH > C)	0.123 (RH > C)	0.0022

*Adjusted for age and smoking

Although only two pulses reached statistical significance ($P \leq 0.05$) in Table XVI-1-9, the consistent directional findings in all peripheral pulses were sufficient to merit additional clarifying analyses. Further, these directional findings were present after accounting for diabetes and the clinically confounding physical effects of peripheral pitting edema and obesity. Accordingly, various aggregates of pulses were constructed to determine more precisely the anatomic patterns of the abnormalities. This approach, adjusted by age and smoking history, is displayed in Table XVI-1-10.

Table XVI-1-10

SUMMARY OF PERIPHERAL PULSE ABNORMALITY COMBINATIONS:
RANCH HANDERS AND ORIGINAL COMPARISONS
ADJUSTED BY AGE AND SMOKING HISTORY
(NON-BLACKS ONLY)

Pulse Abnormalities Combination	Adjusted P Value and Direction of Group Abnormalities	Unadjusted P Value Age Versus Pulse Combination
Leg Pulses* (Femoral, Popliteal, Dorsalis Pedis, Posterior Tibial)	0.0302 (RH > C)	0.0001
All Pulses (Carotid, Femoral, Radial, Popliteal, Dorsalis Pedis, Posterior Tibial)	0.0257 (RH > C)	0.0005
Peripheral Pulses (Radial, Femoral, Popliteal, Dorsalis Pedis, Posterior Tibial)	0.0235 (RH > C)	0.0002

*In nondiabetic, non-Black, Ranch Handers and the original comparisons, leg pulses were associated with a history of intermittent claudication ($P = 0.0113$), and this association was the same in both groups ($P = 0.962$).

The data in Table XVI-1-10 did not point to specific anatomic groupings but rather suggested a generalized phenomenon. As a result of this finding, the pulse data were reanalyzed using testosterone and differential cortisol results as new covariates. No substantial change in the significance of the pulse findings was observed. In order to provide a complete approach to the peripheral pulse findings, 2 supplemental contrasts using other denominators were performed: 1) an analysis of both Black and non-Black Ranch Handers versus Black and non-Black comparisons from the entire comparison group, adjusted for age, smoking history in pack-years, and cholesterol level; and 2) an unadjusted analysis of Black Ranch Handers versus Black comparisons from the entire comparison set. The data from these analyses are presented in Table XVI-1-11.

Table XVI-1-11

SUMMARY OF PERIPHERAL PULSE QUALITY:
ALL RANCH HANDERS VERSUS ALL COMPARISONS*, ASSOCIATION OF AGE,
UNADJUSTED CONTRAST OF BLACK RANCH HANDERS AND BLACK COMPARISONS

	Blacks and Non-Blacks		Blacks Only
Pulse Examined, Number of Participants	P Value and Direction of Group Abnormalities	P Value of Age Association Both Groups**	Unadjusted P Value
Radial N = 1884	0.047 (RH > C)	0.012	0.890
Femoral N = 1882	0.134 (RH > C)	0.007	0.219
Popliteal N = 1883	0.0174 (RH > C)	<0.001	0.219
Dorsalis Pedis N = 1881	0.006 (RH > C)	<0.001	0.789
Posterior Tibial N = 1882	0.067 (RH > C)	<0.001	0.557

*Adjusted for age, smoking, and cholesterol level
**Unadjusted for smoking and cholesterol

The data in Table XVI-1-11 are thus corroborative of diminished pulse quality in the Ranch Hand group. These data also weakly suggest that the Ranch Hand - comparison pulse differences may be aggregated in the non-Black population (or may be spurious due to small sample size). A matched pair analysis (matching variables: age, job, race) of data sets for 3 pulses (see Table XVI-1-9), adjusting for percent body fat and smoking history, are shown in Table XVI-1-12. Due to sparse data, only main effects were included in these analyses.

Table XVI-1-12

MATCHED PAIR ANALYSIS FOR THREE PERIPHERAL PULSES:
RANCH HANDERS VERSUS ORIGINAL COMPARISONS
(NON-BLACKS ONLY)

Pulse Variables	P Value and Direction of Group Abnormalities
Popliteal Pulse	0.053 (RH > C)
Dorsalis Pedis	0.050 (RH > C)
Posterior Tibial	0.081 (RH > C)

Thus, the data in Table XVI-1-12 reaffirm the overall finding of significant peripheral pulse deficits in the Ranch Hand group.

4. Risk Factors in Central and Peripheral Cardiovascular Disease

This section emphasizes cardiovascular disease relationships that are highlighted by significant risk factors or combinations of risk factors identified in the preceding sections or in the general literature.

a. Cholesterol and HDL Cholesterol

Nondiabetic non-Black Ranch Handers and the non-Black original comparisons were contrasted for continuous cholesterol and HDL levels via a general linear model, adjusting for age (<40, ≥40), smoking history (0, 1-10, >10 pack-years), and body fat (<25%, ≥25%). Although no group membership differences were found for cholesterol and HDL, several of the covariates were of profound influence. These data are shown in Table XVI-1-13.

Table XVI-1-13

CHOLESTEROL AND HDL IN
RANCH HANDERS AND ORIGINAL COMPARISONS
(NON-BLACKS ONLY)

Dependent Variable	Adjusted Ranch Hand - Comparison P Value	Covariate P Values		
		Age	Smoking	Body Fat
Cholesterol	0.355	0.038	0.002	0.919
HDL	0.178	0.788	0.028	0.0001

Similar results were found in the contrast of nondiabetic Blacks. Because of small sample size, covariate adjustment was not possible. The contrasts were made by t tests and the results are shown in Table XVI-1-14.

Table XVI-1-14

CHOLESTEROL AND HDL RESULTS IN
RANCH HANDERS AND ORIGINAL COMPARISONS
(BLACKS ONLY)

	Ranch Hand			Comparison			
	N	Mean	Standard Deviation	N	Mean	Standard Deviation	P Value
Cholesterol	49	214.3	34.6	37	209.8	41.3	0.595
HDL	49	55.5	17.2	37	52.4	14.6	0.375

b. Age, Past Smoking, Current Smoking Risk Factors

Several analyses have shown the substantial effects of age and smoking on the cardiovascular system. Because of the unknown influence of antismoking campaigns in recent years on Air Force personnel, the covariate of smoking history (0, 1-10, >10 pack-years) may not be fully appropriate, particularly if smoking ceased several years before the examination. Consequently, all dependent variables were reanalyzed for group differences restricting to older (>40), heavy past smokers (>10 pack-years), adjusted for current smoking (yes, no). These contrasts are presented in Table XVI-1-15. Blacks and diabetics were removed for the analysis.

Table XVI-1-15

RANCH HANDERS AND ORIGINAL COMPARISONS
ADJUSTED FOR CURRENT SMOKING
(NON-BLACKS, $\geq$ 40 YEARS, > 10 PACK YEARS ONLY)

Dependent Variable(s)	P Value and Direction of Group Significance	
Systolic Blood Pressure	0.571	
Diastolic Blood Pressure	0.350	
ECG Abnormalities	0.322	
Heart Sound Abnormalities	0.833	
Eyegrounds	0.628	
Carotid Bruits	0.026	RH > C
Radial Pulse	0.258	
Femoral Pulse	0.033	RH > C
Popliteal Pulse	0.001	RH > C
Dorsalis Pedis Pulse	0.002	RH > C
Posterior Tibial Pulse	0.054	RH > C
All Pulses	0.002	RH > C
Leg Pulses	0.003	RH > C

These specific data, when compared to the broader previous analyses in Table XVI-1-9, show decreasing P values. In addition, there is a suggestion that the peripheral pulse deficits are targeted in the older heavy smokers who are currently still smoking.

c. Reported and Verified Heart Disease

All participants were asked 2 questions during the in-home interview that were intended to capture a history of heart disease. The questions were: "Did you ever have a heart condition?" and "Did you ever have any other major health condition?" All affirmative responses were medically coded by the International Classification of Diseases, 9th Edition, Clinically Modified (ICD CM). Twenty-seven distinct cardiac classifications were identified for the Ranch Hand group and 19 were found in the comparison group. Medical records were sought on all of these individuals in order to verify the reported conditions. Table XVI-1-16 summarizes the verification results for the specific question on past heart disease.

Table XVI-1-16

MEDICAL RECORD VERIFICATION OF REPORTED HEART DISEASE

	Ranch Hand Group	Original Comparison Group
Number of reported cardiac conditions	139	98
Medical Records Reviewed	117	81
Medical Records Pending	-22	-17
% Cardiac Conditions Verified	82.9	85.2
% Cardiac Conditions Unsupported	17.1	14.8

Overall, these data show a high confirmation proportion of reported cardiac conditions. Since Table XVI-1-16 does not include results from the second overlapping question (Other major conditions?) and since individuals may have multiple heart disease responses, the following analyses have different numerators and denominators.

All Ranch Handers (diabetics, Blacks, edemics included) were contrasted to the original comparisons for reported heart disease and reported heart attacks. This analysis was supplemented by an analysis on verified heart disease and heart attacks; all these data are summarized in Table XVI-1-17. The unadjusted relative risk and 95% confidence interval for verified heart disease are 1.00 and (.79, 1.27).

Table XVI-1-17

RANCH HAND AND ORIGINAL COMPARISON GROUPS
VERSUS REPORTED AND VERIFIED HEART DISEASE AND HEART ATTACKS

Heart Disease Parameter	Ranch Hand Yes	Ranch Hand No	Comparison Yes	Comparison No	P Value
Reported Heart Disease	181	864	136	637	0.878
Reported Heart Attack	10	1035	4	769	0.296
Verified Heart Disease	147	898	109	664	0.982
Verified Heart Attack	7	1038	3	770	0.432

While the lack of group differences in Table XVI-1-17 is of interest, and the good agreement between subjective responses and medically verified responses is notable, additional covariate analyses were conducted to rule out any hidden effect of a risk factor interaction that might be associated with group membership. Thus, Ranch Handers and their comparisons were again contrasted for reported heart disease and verified heart disease, adjusting for the covariates of age, smoking, body fat or HDL. As age was confounding for both reported and verified disease, the analyses are age specific. Further, there are significant interactions between smoking, group membership, and disease; these findings are shown in Table XVI-1-18.

Table XVI-1-18

RANCH HAND AND ORIGINAL COMPARISON GROUP:
COVARIATE ANALYSES OF REPORTED AND VERIFIED HEART DISEASE

Parameter and Covariates		Adjusted Intergroup P Value and Direction of Association	
Reported Heart Disease:*			
Body Fat, smoking	<40	0.530	(RH = C)
	**≥40, less than 10 pack-years	0.0038	(RH < C)
	≥40, greater than 10 pack-years	0.139	(RH = C)
Verified Heart Disease*			
HDL, smoking	<40	0.506	(RH = C)
	***≥40, less than 10 pack-years	0.008	(RH < C)
	≥40, greater than 10 pack-years	0.0712	(RH > C)

*Age confounding variable
**Group - heart disease - smoking interaction: P = 0.0054
***Group - heart disease - smoking interaction: P = 0.0047

These data, in contrast to Table XVI-1-17, demonstrate associations of significance. Young Ranch Handers are equivalent to their young comparisons for both reported and verified heart disease; whereas, the older Ranch Handers smoking more than 10 pack-years are manifesting more verified heart disease than their counterparts. Conversely, older Ranch Handers smoking less than 10 pack-years are faring significantly better than their comparisons for both reported and verified heart disease. These associations, in light of essentially negative blood pressure and ECG findings at the physical examination, could be speculatively attributed to a wide array of post hoc explanations: e.g., a true disease process that will evolve more clearly in the future, an enigmatic finding akin to the peripheral pulse deficits, chance, etc.

d. Cardiovascular Examination Findings and Verified Historical Heart Disease

The cardiovascular examination findings were contrasted to the history of cardiovascular disease as verified by detailed medical record review. The purposes of this analysis were to determine the degree of positive correlation between the examination and the past medical history, and to determine if peripheral pulse abnormalities were associated with known cardiovascular disease. These data are presented in Table XVI-1-19.

Table XVI-1-19

ASSOCIATION OF CENTRAL AND PERIPHERAL CARDIOVASCULAR ABNORMALITIES WITH VERIFIED HEART DISEASE BY AGE: RANCH HANDERS VERSUS ORIGINAL COMPARISONS* (NON-BLACKS ONLY)

Dependent Variable	P Value (Unadjusted) Dependent Variable Versus Verified Heart Disease	P Value (Adjusted for Age) Ranch Hand VersusComparison
Systolic Blood Pressure	<0.00001	0.229
Diastolic Blood Pressure	<0.00001	0.391
Electrocardiogram	<0.00001	0.875
Heart Sounds	0.292	0.316
Carotid Bruits	0.084	0.223
Radial Pulse	0.023	0.152
Femoral Pulse (≥40)	0.147	0.104
Posterior Tibial Pulse (>40)	0.103	0.082
Popliteal Pulse (≥40)	0.074	0.022
Dorsalis Pedis Pulse (≥40)	0.002	0.094
All Pulses (<40)	0.0004	0.205
(≥40)		0.0691
Peripheral Pulses (<40)	0.0007	0.261
(≥40)		0.048
Leg Pulses (<40)	0.0023	0.369
(≥40)		0.044

*Pitting edema omitted for pulse analyses

Systolic, diastolic blood pressure and ECG abnormalities at physical examination showed exceptionally significant ($P \approx 0$) associations with medical record histories of cardiac disease, regardless of group membership or age. While moderately positive associations are to be expected, the unusual strength of the associations suggests that very few new cases of hypertension or ECG abnormalities were diagnosed at examination, reflecting perhaps, up-to-date medical records due to the overall medical sophistication and free access to medical care by most members of both groups. The association of carotid bruits and previously diagnosed cardiovascular disease was marginally positive but based upon small numbers. Table XVI-1-19 was most revealing for the peripheral pulse abnormalities. For the radial pulse, the data were too sparse for age adjustment but for all other pulse abnormalities, age was confounding, primarily due to a relative lack of abnormalities in the under-40 age group. A remarkably consistent observation in the 40-and-older age group was that significant or borderline significant Ranch Hand - comparison differences were found almost exclusively in those individuals without a history of cardiovascular disease. This uniform pattern is best exemplified by the popliteal pulse data, as shown in Table XVI-1-20.

Table XVI-1-20

ASSOCIATION OF POPLITEAL PULSE ABNORMALITIES
WITH VERIFIED HISTORY OF CARDIOVASCULAR DISEASE BY AGE AND GROUP MEMBERSHIP*

History of Cardiovascular Disease	Group Membership	Popliteal Pulse Findings in ≥40 Age Group: Abnormal	Normal
Yes (Verified by record review)	Ranch Hand	2	68
	Comparison	2	59
No	Ranch Hand	11	404
	Comparison	0	313

Popliteal pulse by disease history: $P = 0.074$
Popliteal pulse by disease by group interaction: $P = 0.022$

*No pulse abnormalities in <40 group

Interpretation of this intriguing finding at the baseline physical examination is not clear. The fact that the abnormal pulses, regardless of group membership, are associated with increased age, heavy past smoking, current smoking (and possibly race), and verified past heart disease and are largely substantiated by the use of 3 related denominators suggest that the finding is real rather than spurious. While there was most likely a tendency to diagnose additional abnormal pulses, given the first abnormal pulse, this possible examination bias would not likely aggregate in the Ranch Hand group (because of the blind examination) nor in individuals without a history of prior cardiovascular disease. The speculative interpretation of concern is that the finding of substantial "subclinical" peripheral pulse abnormalities (i.e., without a history of past cardiovascular disease) in the Ranch Handers may be a precursor to either clinically manifest arterial disease or central cardiovascular abnormalities. This possibility will receive detailed attention at the first follow-up examination because an analysis of onset times for verified heart disease (adjusted for race, occupation, and age) did not show a significant difference between the Ranch Hand and comparison group (P = 0.395). This finding suggests that if the observed pulse abnormalities are a precursor to central cardiovascular disease, this pathogenesis is not manifested by premature heart disease at this time.

5. Exposure Index Analyses

All of the dependent variables within the Ranch Hand group were compared to the exposure index. Systolic and diastolic blood pressure elevations, and ECG, heart sound, and eyeground abnormalities were adjusted for age (<40, ≥40). The peripheral pulse analyses were not age adjusted because of sparse data; subjects with peripheral pitting edema were omitted from these comparisons. The exposure index was stratified into 3 categories: low, medium, and high. All analyses were performed on each of 3 occupational categories: officer, flying enlisted, and ground enlisted. This analysis is presented in Table XVI-1-21. Separate age analyses were performed when age was found to be a confounding variable. When some data were too small for valid analysis, the word sparse is written instead of a P value.

Table XVI-1-21

SUMMARY OF EXPOSURE INDEX ANALYSES WITHIN THE RANCH HAND GROUP*

		P Value		
		Adjusted for Age	Age	
Dependent Variable**	Occupation	(***=Unadjusted for Age)	<40	≥40
Systolic Blood Pressure	Officer		0.560	0.746
	Flying Enlisted	0.731		
	Ground Enlisted		0.499	0.701
Diastolic Blood Pressure	Officer		Sparse	0.739
	Flying Enlisted	0.313		
	Ground Enlisted		0.567	0.214
ECG	Officer	0.858		
	Flying Enlisted	0.209		
	Ground Enlisted	0.450		
Heart Sounds	Officer	0.397***		
	Flying Enlisted	0.395***		
	Ground Enlisted		0.255	0.638

Table XVI-1-21 (Cont'd)

SUMMARY OF EXPOSURE INDEX ANALYSES WITHIN THE RANCH HAND GROUP[1]

		P Value		
		Adjusted for Age	Age	
Dependent Variable**	Occupation	(***=Unadjusted for Age)	<40	≥40
Eyegrounds	Officer	0.513		
	Flying Enlisted	0.395***		
	Ground Enlisted		0.255	0.638
Carotid Bruits	Officer	0.616		
	Flying Enlisted	0.992		
	Ground Enlisted	0.094		
Popliteal Pulse	Officer	Sparse		
	Flying Enlisted	Sparse		
	Ground Enlisted	0.814		
Dorsalis Pedis Pulse	Officer	0.288		
	Flying Enlisted	0.719		
	Ground Enlisted	0.531		
Posterior Tibial Pulse	Officer	0.643		
	Flying Enlisted	Sparse		
	Ground Enlisted	0.654		
All Pulses	Officer	0.305		
	Flying Enlisted	0.624		
	Ground Enlisted	0.624		
Peripheral Pulses	Officer	0.338		
	Flying Enlisted	0.784		
	Ground Enlisted	0.746		
Leg Pulses	Officer	0.350		
	Flying Enlisted	0.784		
	Ground Enlisted	0.882		

*Peripheral edema omitted for peripheral pulse analyses
**Radial and femoral pulses omitted; data too sparse
***Unadjusted for age.

The data in Table XVI-1-21 clearly indicate that there is no detectable association between the herbicide exposure index adjusted by occupational category and any of the cardiovascular variables.

6. Summary

Central cardiovascular system abnormalities, as manifested by elevated systolic or diastolic blood pressure, abnormal ECG's, and abnormal heart sounds, showed no statistically significant Ranch Hand - comparison group differences, but did reflect a strong correlation to increased age and, to a lesser degree, heavy past smoking. The 3 risk factors of age, smoking, and cholesterol were strongly associated with each other. Unadjusted analyses of Blacks were essentially negative. The prevalence of funduscopic abnormalities and carotid bruits was not associated with group membership but was significantly dependent upon age.

Abnormal peripheral pulses were associated with the Ranch Hand group. A series of detailed covariate analyses showed that pulse abnormalities, regardless of group membership, were associated with increased age (≥40 years), heavy past smoking, current smoking, and a verified history of past cardiovascular disease. Substantial Ranch Hand pulse abnormalities were also found in members without prior cardiovascular disease. All significant or borderline significant pulse findings in the Ranch Handers were largely sustained regardless of the comparison group used (originals, matched originals, or all comparisons). Both the femoral and carotid pulses revealed substantial, but statistically nonsignificant, abnormalities in the Ranch Hand group. More biologic credence is assigned to the large artery observations in light of the small artery findings. Peripheral pulse abnormalities will merit extensive clinical inquiry at the first follow-up examination. The history of cardiovascular disease obtained during the in-home interview was verified by a review of medical records. Both reported and verified past heart disease and heart attacks were adjusted by age, smoking, and body fat or HDL. This analysis revealed that the older (≥40 years) smoking Ranch Handers manifested significantly more verified heart disease than their equivalent comparisons. Alternatively, the older less smoking Ranch Handers have substantially less reported and verified cardiovascular disease than their comparisons. Detailed herbicide exposure analyses showed no associations to any of the central or peripheral cardiovascular findings. Future reports will explore a theoretical synergism between cigarette smoking and herbicide exposure.

Chapter XVI-2

IMMUNOLOGY

1. Introduction

Recent experimental data in animals have suggested that TCDD has deleterious effects on the immune system (Dean et al, 1984). As a result, the Science Panel Committee recommended that the immunotoxic potential of TCDD be evaluated during the physical examination portion of this study. Parameters selected for assessment included: (1) the enumeration of T-lymphocytes, T-lymphocyte subsets and B-lymphocytes using monoclonal surface marker analysis and (2) functional ability of lymphocyte to respond to selected antigen or mitogen stimuli in the lymphocyte transformation assay.

Five hundred ninety-two participants were randomly selected for this examination using the terminal digit of the participant's case number. This selection occurred during the time period March 1982 through September 1982. Of the 592 participants, 297 were Ranch Handers and 295 were comparisons. Of the 295 comparisons, 180 were original comparisons. The statistical testing presented in this chapter is all based on this basic set of 297 Ranch Handers and 180 original comparisons. However for each test performed, differing data deletions occurred. Specifically, data from professed homosexuals were removed from all analyses. Also, data were removed from all analyses if covariate information (age, smoking, alcohol use) was missing. Finally, data were removed from certain analyses (T_{11}, T_3, T_4, T_8, T_4/T_8, B_1 counts and percentages) if: (1) differential counts were unavailable, (2) if samples exhibited greater than 30% background fluorescence, or (3) if samples had a T_3 or T_{11} proportion of less than 10%.

Surface marker analysis and lymphocyte function studies were performed on purified mononuclear cells obtained from heparinized whole blood drawn at Kelsey-Seybold Clinic early on the second day of the examination period. Peripheral blood mononuclear leukocytes (PBL) were separated from erythrocytes and polymorphonuclear leukocytes using a density gradient centrifugation technique. Unfortunately, blood specimens were collected and processed in glass tubes with resultant variable loss of adherent PBL. White cell differential counts were not obtained on purified PBL so that the number of lymphocytes actually placed into functional assays could not be ascertained. Due to these laboratory difficulties, coupled with relatively small sample sizes, exposure index analyses are not provided in this chapter.

2. Analysis of Immunological Cell Count Data

Mouse monoclonal antibodies directed against various lymphocyte surface antigens were incubated with PBL. Following washing, fluorescent anti-mouse antibodies were added. After the cells had been stored for a variable period in paraformaldehyde, the presence or absence of fluorescent antibody on each PBL was determined and counted using a cytofluorograph. The percentage of cells positive for each surface marker is reported as the number of fluorescent cells divided by the total number of lymphocytes in a given specimen. Since differential counts were not obtained on the purified PBL, a 250 cell differential count was performed at the recommendation of the Peer Review Committee on paraformaldehyde-fixed cells. These cells had been stored for 6 to 12 months. Although cell morphology was not optimal, determination of the percentage of lymphocytes in each specimen was possible. The number of surface marker positive cells per mm^3 was calculated by multiplying the percent marker positive cells by the total lymphocyte count.

The cells counted and analyzed for this report are classified as having T_{11}, T_3, T_4, T_8, or B_1 cell surface markers. The T_{11} surface marker identifies thymus dependent lymphocytes which form rosettes with sheep erythrocytes (also called E^+ cells). The T_3 surface marker is found on nearly 100% of circulating T-lymphocytes cells (Reinherz and Schlossman, 1980). Cells with T_4 cell surface markers proliferate in response to soluble antigens and have an inducer or helper function in T-T, T-B and T-macrophage interactions (Reinherz and Schlossman, 1980). T_8 cells have cytotoxic and suppressor functions (Reinherz and Schlossman, 1980). B1 cells, or bursa equivalent cells, are producers of immunoglobulins (David, 1979).

The number of T_{11}, T_3, T_4, T_8, and B_1 positive cells per mm^3 are provided below by group, along with the T_4/T_8 ratio and total lymphocyte count. Additionally, percentages of T_{11}, T_3, T_4, T_8, and B_1 positive cells are reported by group. The data were analyzed for statistically significant group differences using the Kolmogorov-Smirnov Two Sample Test. Also, crude group (Ranch Hand versus comparison) means were contrasted, and then the groups were contrasted while adjusting for age, smoking history in pack-years and alcohol intake measured as drink-years. The literature does not yet provide clear guidance to the selection of covariates for analysis as attempted here. Age, smoking and alcohol were chosen based on the observation that these variables frequently correlate with general measures of health and impact upon hematologic parameters. Group interactions with age, smoking or alcohol indicate group differences associated with these covariables. When group-covariate interaction is observed, group and associated covariate main effects are not reported, rather the interaction is detailed. The probability level used to indicate an interaction of interest is $P = 0.100$. In the absence of interaction, group and covariate main effects are reported in the usual manner. When $P > 0.100$ for all interactions, P values for the reduced model, consisting of main effects only, are provided.

Table XVI-2-1 provides the results of Kolmogorov-Smirnov testing of the number of surface marker positive cells per mm^3. A borderline statistical difference is seen in the B_1 count with Ranch Handers having lower values. However, B_1 cells are an adherent set of cells. The purification process resulted in a variable loss of adherent cells, therefore, this data must be interpreted with extreme caution. Table XVI-2-2 provides the Kolmogorov-Smirnov testing of cell percentages and no statistically significant differences are observed. Table XVI-2-3 provides unadjusted means for the number of surface marker positive cells per mm^3. No statistically significant group mean differences are observed. Table XVI-2-4 provides unadjusted means for the cell percentages, and again no statistically significant group mean differences are observed. Both counts and percentages are provided to aid with interpretation.

Table XVI-2-1

KOLMOGOROV-SMIRNOV TESTING OF NUMBER OF SURFACE MARKER POSITIVE CELLS (THOUSANDS/mm^3)

Variable	Group	N	Percentiles 10%	50%	90%	P Value
T_{11}	COMP	144	0.77	1.23	2.02	0.74
	RH	235	0.70	1.25	1.96	
T_3	COMP	144	0.73	1.28	2.13	0.39
	RH	233	0.70	1.27	1.96	
T_4	COMP	147	0.48	0.78	1.42	0.81
	RH	231	0.398	0.794	1.251	
T_8	COMP	147	0.277	0.604	1.168	0.34
	RH	235	0.296	0.569	0.985	
T_4/T_8	COMP	147	0.64	1.38	2.62	0.78
	RH	231	0.64	1.41	2.70	
B_1	COMP	147	0.022	0.071	0.247	0.097
	RH	235	0.023	0.071	0.188	
TLC	COMP	177	1.35	1.91	2.74	0.63
	RH	290	1.34	1.92	2.54	

COMP = comparison group
RH = Ranch Hand group

Table XVI-2-2

KOLMOGOROV-SMIRNOV TESTING OF PERCENTAGE OF SURFACE MARKER POSITIVE CELLS (THOUSANDS/mm^3)

Variable	Group	N	Percentiles 10%	50%	90%	P Value
T_{11}	COMP	144	42.0	66.0	87.5	0.90
	RH	235	41.6	68.0	88.4	
T_3	COMP	144	48.5	66.5	83.5	0.79
	RH	233	48.4	66.0	83.6	
T_4	COMP	147	26.8	42.0	58.0	0.45
	RH	231	23.0	44.0	61.0	
T_8	COMP	147	17.8	31.0	47.0	0.82
	RH	235	16.6	29.0	49.0	
B_1	COMP	147	1.0	3.0	13.2	0.48
	RH	235	1.0	4.0	10.4	

COMP = comparison group
RH = Ranch Hand group

Table XVI-2-3

UNADJUSTED MEANS FOR NUMBER OF SURFACE MARKER POSITIVE CELLS (THOUSANDS/mm) AND P VALUES FOR TESTS BETWEEN GROUPS MEANS

Variable	Group	N	Unadjusted Means	SEM	P Values
T_{11}	COMP	139	1.33	0.050	0.47
	RH	228	1.29	0.034	
T_3	COMP	139	1.36	0.052	0.21
	RH	226	1.29	0.031	
T_4	COMP	142	0.877	0.038	0.49
	RH	224	0.846	0.027	
T_8	COMP	142	0.660	0.029	0.11
	RH	228	0.606	0.020	
T_4/T_8	COMP	142	1.54	0.075	0.34
	RH	224	1.65	0.075	
B_1	COMP	142	0.117	0.011	0.26
	RH	228	0.102	0.008	
TLC	COMP	171	2.00	0.046	0.14
	RH	280	1.92	0.028	

COMP = comparison group
RH = Ranch Hand group
TLC = total lymphocyte count
SEM = standard error of the means

Table XVI-2-4

UNADJUSTED MEANS FOR PERCENTAGE OF SURFACE MARKER POSITIVE CELLS AND P VALUES FOR TESTS BETWEEN GROUPS MEANS

Variable	Group	N	Unadjusted Means	SEM	P Values
T_{11}	COMP	139	65.0	1.44	0.71
	RH	228	65.7	1.20	
T_3	COMP	139	65.6	1.22	0.75
	RH	226	65.1	0.97	
T_4	COMP	142	42.1	1.13	0.53
	RH	224	43.1	1.07	
T_8	COMP	142	32.0	1.02	0.36
	RH	228	30.8	0.80	
B_1	COMP	142	5.80	0.50	0.48
	RH	228	5.35	0.41	

COMP = comparison group
RH = Ranch Hand group
SEM = standard error of the means

Table XVI-2-5 provides the adjusted surface marker positive cell count means, along with P values for main (group, age, smoking and alcohol) and interaction (group by age, group by smoking, and group by alcohol) effects. No main or interaction effect associated with group is noted to be statistically significant.

The number of lymphocytes and T_8 positive cells per mm^3 decreased with increasing age in both the Ranch Hand and comparison groups. The effect was -0.0043 thousand cells per mm^3 per year of life for T_8 and was -0.0110 thousand cells per mm^3 per year of life for the lymphocyte count. Smoking was observed to be associated with increased cell counts on all variables except for B_1 positive cells. Specifically, the slope was 0.0036 thousand cells per mm^3 per pack-year for T_{11}; 0.0076 thousand cells per mm^3 per pack-year for T_3; 0.0070 thousand cells per mm^3 per pack-year for T4; 0.0022 thousand cells per mm^3 per pack-year for T_8; and 0.0083 thousand cells per mm^3 per pack-year for total lymphocyte count.

Table XVI-2-5

ADJUSTED MEANS, PLUS MAIN AND INTERACTION P VALUES FOR THE NUMBER OF MARKER POSITIVE CELLS (THOUSANDS/mm^3)

					P Values for					
Variable	Group (Gp)	N	Adj'd Mean	P Value for Adj'd Means	Age Effect	Smkng Effect	Alco Effect	Gp x Age Effect	Gp x Smkng Effect	Gp x Alco Effect
T_{11}	COMP	139	1.33	0.52	-	0.029	-	-	-	-
	RH	228	1.29							
T_3	COMP	139	1.35	0.38	-	<0.001	-	-	-	-
	RH	226	1.30							
T_4	COMP	142	0.864	0.82	-	<0.001	-	-	-	-
	RH	224	0.854							
T_8	COMP	142	0.660	0.12	0.057	0.025	-	-	-	-
	RH	228	0.606							
T_4/T_8	COMP	142	1.52	0.22	-	-	-	-	-	-
	RH	224	1.66							
B_1	COMP	142	0.117	0.27	-	-	-	-	-	-
	RH	228	0.102							
TLC	COMP	171	1.99	0.20	<0.001	<0.001	-	-	-	-
	RH	280	1.92							

COMP = comparison group
RH = Ranch Hand group
\- = P > 0.050 for main effects or P > 0.100 for interactions. When P > 0.100 for all interactions, P values for the reduced model, consisting of main effects only, are provided.
TLC = total lymphocyte count

Table XVI-2-6 shows adjusted means for percentage of surface marker positive cells. No statistically significant overall group differences are observed. The T_3 and T_4 percentages are influenced by smoking, but this effect is essentially the same in both study groups. The effect of smoking on the T_3 percentage is 0.124 percentage points per pack-year, while the effect of smoking on the T_4 percentage is 0.171 percentage points per year. A weak indication of a group specific alcohol intake effect was noted on the T_{11} percentage. The association of alcohol use with the percentage of T_{11} positive cells was 0.0980% per drink-year in the comparison group and -0.0042% per drink-year in the Ranch Hand group. This pattern could reflect a diminished Ranch Hand immunological response to drinking in reference to the comparisons; the biological relevance of this borderline finding is uncertain at this time.

Table XVI-2-6

ADJUSTED MEANS AND OTHER MAIN AND INTERACTION EFFECTS FOR PERCENTAGE OF SURFACE MARKER POSITIVE CELLS

Variable	Group (Gp)	N	Adj'd Mean	P Value for Adj'd Means	Age Effect	Smkng Effect	Alco Effect	Gp x Age Effect	Gp x Smkng Effect	Gp x Alco Effect
T_{11}	COMP	139	*	*	-	-	-	-	-	0.087
	RH	226								
T_3	COMP	139	65.2	0.92	-	0.005	-	-	-	-
	RH	226	65.4							
T_4	COMP	142	41.6	0.27	-	<0.001	-	-	-	-
	RH	224	43.4							
T_8	COMP	142	32.0	0.34	-	-	-	-	-	-
	RH	228	30.7							
B_1	COMP	142	5.79	0.52	-	-	-	-	-	-
	RH	228	5.36							

COMP = comparison group
RH = Ranch Hand group
* = that a group interaction effect was noted rendering overall group mean differences and the associated main effect not meaningful.
\- = P > 0.050 or P > 0.100 per footnote in Table XVI-2-3.

In summary, the lymphocyte surface marker analyses reported in Tables XVI-2-5 and XVI-2-6 show no detectable differences between the Ranch Hand and comparison groups on these measures, except possibly for the borderline group difference in the T_{11} percentage by alcohol use association.

3. T and B Cell Functional Studies

T and B lymphocyte function was determined by measuring the ability of these cells to transform in response to antigen or mitogen stimuli. Briefly, this assay is performed by culturing PBL in the presence of mitogens (plant lecthins which stimulate the cells to divide) or antigen. After a certain length of incubation time, the rate of DNA synthesis is estimated by adding tritiated thymidine (a radioactive DNA precursor). Thus, the counts per minute of thymidine incorporated into the cell culture is a measure of the ability of those lymphocyte to proliferate in response to the added stimulus. Mitogens stimulate lymphocytes non-specifically. Phytohemagglutin (PHA) and concanavallin A (conA) stimulate T-lymphocytes to divide, while pokeweed mitogen (PW) stimulates B-lymphocytes through a T-lymphocyte. On the other hand, antigen require that lymphocytes recognize specifically antigen as a substance to which the host has been exposed. Tetanus toxoid (TT) is a T-lymphocyte dependent B-lymphocyte recall antigen.

Kolmogorov-Smirnov testing of the 4 stimulation and 2 control measurements are shown in Table XVI-2-7. No statistically significant group differences are noted. Unadjusted group mean net counts per minute for the stimulation studies and control measurements are shown in Table XVI-2-8. No statistically significant group differences are noted except in Control #1 where the Ranch Hand group was found to have a lower unstimulated proliferation rate. A comparable differential is also noted in Control #2, but is not statistically significant. The group differences noted are of unknown biological significance.

Table XVI-2-7

KOLMOGOROV-SMIRNOV TESTING OF T AND B CELL FUNCTIONAL STUDIES

Variable	Group	N	Percentiles 10%	50%	90%	P Value
Control #1	COMP	168	138	448	1483	0.20
	RH	279	140	374	1320	
After conA	COMP	168	13596	58394	99104	0.38
	RH	279	17741	54190	91724	
After PHA	COMP	168	30143	84339	135684	0.51
	RH	279	33027	79342	130064	
Control #2	COMP	168	142	404	1079	0.85
	RH	274	132	388	917	
After PW	COMP	168	12232	27916	53662	0.64
	RH	274	12700	29623	58288	
After TT	COMP	168	1001	3719	16058	0.81
	RH	274	866	3726	13979	

COMP = comparison group
RH = Ranch Hand group

Table XVI-2-8

UNADJUSTED MEANS FOR T AND B CELL FUNCTIONAL STUDIES BY GROUP, AND P VALUES FOR TESTS BETWEEN GROUP MEANS

Variable	Group	N	Unadjusted Means (nCPM)	SEM	P Value for Unadj'd Means
Control #1	COMP	163	652	49.2	0.031
	RH	269	535	29.4	
After conA	COMP	163	57454	2248	0.31
	RH	269	54637	1658	
After PHA	COMP	163	83808	3048	0.37
	RH	269	80433	2244	
Control #2	COMP	163	523	37.1	0.31
	RH	264	480	23.9	
After PW	COMP	163	32092	1337	0.37
	RH	264	33710	1151	
After TT	COMP	163	6848	650	0.86
	RH	264	7051	787	

COMP = comparison group
RH = Ranch Hand group
nCPM = net counts per minute (stimulated CPM - control CPM).
SEM = standard error of the mean

Table XVI-2-9 shows adjusted net CPM means. A statistically significant group difference is noted in Control #1. Other group effects are noted as interactions with smoking and alcohol. Specifically, smoking was associated with a decreased proliferation rate to concanavallin A stimulation,(-113 nCPM per pack-year) in the comparison group, while smoking was associated with an increased proliferation rate in the Ranch Hand cohort (+169 CPM per pack-year). Two comparable group differences were observed as interactions of concanavallin A and phytohemagglutinin stimulation with alcohol use. Alcohol use was associated with an increased proliferation after concanavallin A stimulation in the comparison group (+212 CPM per drink-year), while an increase of 12 CPM per drink-year was found in the Ranch Hand cohort. Alcohol use in the comparison group increased proliferation after phytohemagglutinin by 167 CPM per drink-year, while alcohol use in the Ranch Hand group decreased proliferation by 76 CPM per drink-year. This alcohol effect has no known biologic explanation. The finding is of questionable significance and will need to be examined further in subsequent immunologic analyses.

In addition to these group specific effects, some effects not associated with group were observed. Age and smoking were covariates which were found to be highly statistically significant. Lymphoproliferative responses to phytohemagglutinin and concanavallin A decreased monotonically in both Ranch Hand and comparison groups with advancing age. Lymphocyte response to pokeweed mitogen increased with increasing pack-years in both Ranch Hand and comparison groups.

Table XVI-2-9

ADJUSTED MEANS, PLUS MAIN AND INTERACTION P VALUES FOR T AND B CELL FUNCTIONAL STUDIES BY GROUP

Variable	Group (Gp)	N	Adj'd Mean	P Value for Adj'd Means	Age Effect	Smkng Effect	Alco Effect	Gp x Age Effect	Gp x Smkng Effect	Gp x Alco Effect
Control #1	COMP	163	657	0.023	-	-	-	-	-	-
	RH	269	532							
After conA	COMP	163	*	*	<0.001	*	*	-	0.089	0.025
	RH	269	*	*						
After PHA	COMP	163	*	*	<0.001	-	*	-	-	0.041
	RH	269	*	*						
Control #2	COMP	163	518	0.41	-	-	-	-	-	-
	RH	264	484							
After PW	COMP	163	31982	0.32	-	0.01	-	-	-	-
	RH	264	33778							
After TT	COMP	163	6929	0.95	-	-	-	-	-	-
	RH	264	7001							

COMP = comparison group
RH = Ranch Hand group
\- = P > 0.050 or P > 0.100 per footnote in Table XVI-2-3.

4. Summary

The analysis of these data has provided a valuable insight into the rapidly changing area of clinical immunology. Analysis has revealed no statistically significant differences in mean T_{11}, T_3, T_4, T_8, T_4/T_8 ratio or B_{11} counts between the Ranch Hand and comparison groups. Similarly, there were no statistically significant overall mean differences in PHA, conA, PW, or TT stimulation responses between the groups. There were significant differences in unstimulated (control) thymidine incorporation ($P = 0.023$) with less activity in the Ranch Hand group. In both groups, lymphoproliferative responsiveness to PHA and conA decreased significantly with increasing age, and total lymphocyte counts were correlated with age and smoking. The subsets of T-lymphocytes (T_3, T_4, T_8, and T_{11}) also were correlated with smoking.

From the clinical vantage point, the immunological findings do not present a picture indicative of immunological alteration in the herbicide-exposed group. However these data are of such quality that concern must be taken for a possibility of both false positive and false negative statements. Due to previously defined difficulties in surface marker analyses and lymphocyte stimulation assays, these data cannot be reliably referenced to other published data. Nonetheless, no gross adverse immunological effects were noted between the herbicide-exposed group and the comparison group.

Chapter XVI-3

HEMATOLOGICAL VARIABLES

In this section, 8 hematological variables are reported. These 8 variables are listed in Table XVI-3-1 along with abbreviations used, units of measure, and normal ranges employed in the analyses. Ranch Hand-comparison group differences have been analyzed using general linear models with all variables except the group indicator treated as continuous variables. Group differences have also been evaluated using log-linear models with all variables treated as categorical. In both the general linear and log-linear model analyses, the hematological variables were adjusted for smoking history available from the questionnaire as pack-years of cigarette use (Wintrobe, 1974). In the general linear models analyses, pack-years were used directly as a continuous variable. In the log-linear models, smoking history was treated as a tricotomous variable by grouping together: (1) nonsmokers, (2) smokers with 10 pack-years or less contact, and (3) smokers with greater than 10 pack-years cigarette smoking. Also, in the log-linear models analyses, the dependent (hematologic) variable was dichotomized as normal (within range) or abnormal (out of range). Analyses using the exposure index were also accomplished using the Ranch Hand participant data. These within-group analyses were performed in much the same manner as the Ranch Hand-comparison group contrasts, except that in the within-group analyses, exposure category took the place of the cohort indicator. Data on all Ranch Hand and original comparison participants are presented in this section.

Table XVI-3-1

HEMATOLOGICAL VARIABLES STUDIED

Variable Name	Abbreviation	Units Of Measure	Normal Range
Red Blood Cell Count	RBC	Million per Cubic mm	4.6 - 6.2
White Blood Cell Count	WBC	Thousand per Cubic mm	4.8 - 10.8
Hemoglobin	Hgb	Grams per 100 ml	14.0 - 18.0
Hematocrit	Hct	ml/100 ml	42.0 - 52.0
Mean Corpuscular Volume	MCV	Cubic Micra	80.0 - 101.0
Mean Corpuscular Hemoglobin	MCH	Micromicrogram	27.0 - 31.0
Mean Corpuscular Hemoglobin Concentration	MCHC	Percent	32.0 - 36.0
Platelet Count	PLT	Thousands Per Cubic mm	150 - 450

Table XVI-3-2 provides the results of the Ranch Hand - comparison group contrasts. The abbreviation CC is used to denote linear model analyses on continuously distributed data, DD denotes categorical log linear analyses.

Two group differences are seen in Table XVI-3-2. The Ranch Hand group has a statistically significantly larger red blood cell corpuscular volume than does the comparison group (P = 0.05 in the CC analysis) and, perhaps paralleling this finding on corpuscular volume, the Ranch Hand group has a larger mean corpuscular hemoglobin (P = 0.04 in the CC analysis).

In performing these analyses of group differences, smoking history was an important variable in essentially all instances. All of the hematological variables except RBC and MCHC increase with cigarette use. A summary of P values and slopes is provided in Table XVI-3-3.

In Table XVI-3-4 analyses are provided within the Ranch Hand group, examining for differences between exposure categories. Sample sizes in these analyses are provided in Table XVI-3-5. Table XVI-3-6 provides variable means and percents by occupation and exposure group.

Table XVI-3-2

P VALUES FOR RANCH HAND-COMPARISON GROUP DIFFERENCES, ADJUSTED MEANS, AND ABNORMAL PERCENTAGES

Var	Anal	Group	Pack-yr	Group x Pack-yr	RH Adj'd Mean	Comp. Adj'd Mean	RH ABN %	Com ABN %
RBC	CC	0.62	0.08	0.65	5.20	5.21	NA	NA
	DD	0.36		0.71	NA	NA	7.43	6.28
WBC	CC	0.14	<0.001	0.48	7.51	7.38	NA	NA
	DD	0.62		0.83	NA	NA	12.45	11.65
HGB	CC	0.15	<0.001	0.77	16.04	15.97	NA	NA
	DD	0.97		0.65	NA	NA	3.28	3.27
HCT	CC	0.23	<0.001	0.25	46.16	46.01	NA	NA
	DD	0.62		0.32	NA	NA	8.30	7.59
MCV	CC	0.05	<0.001	0.58	89.04	88.60	NA	NA
	DD	0.70		0.71	NA	NA	3.76	3.40
MCH	CC	0.04	<0.001	0.73	30.83	30.66	NA	NA
	DD	0.005		0.64	NA	NA	46.24	39.66
MCHC	CC	0.63	0.005	0.15	34.68	34.66	NA	NA
	DD	0.47		0.84	NA	NA	9.46	10.47
PLT	CC	0.06	<0.001	0.76	276.74	271.48	NA	NA
	DD	0.16		0.33	NA	NA	1.16	1.97

Table XVI-3-3

SMOKING EFFECTS ON HEMATOLOGIC VARIABLES
AS SEEN BY CONTINUOUS VARIABLE LINEAR MODELS

Variable	P Value for Smoking Effect	Dependent Variable Smoking Slope (Units/Pack-yr)
RBC	0.08	-0.00089
WBC	<0.001	0.0389
HGB	<0.001	0.00743
HCT	<0.001	0.0266
MCV	<0.001	0.0675
MCH	<0.001	0.0200
MCHC	0.005	-0.00376
PLT	<0.001	0.322

Table XVI-3-4

P-VALUES FOR RANCH HAND OCCUPATION AND EXPOSURE GROUP ANALYSES

	Generalized Linear Model				Log Linear Model		
Var	Occ Cat	Exp Effect	Pack-yr Effect	Exp X Pack-yr	Exp Effect	Pack-yr Effect	Exp X Pack-yr
RBC	OFF	0.69	0.83	0.53	*	*	0.09
	ENL F.	*	*	0.03	0.83	0.66	0.59
	ENL G.	0.06	0.13	0.26	0.35	0.50	0.22
WBC	OFF	*	*	<0.001	0.52	0.47	0.62
	ENL F.	0.61	<0.001	0.26	0.51	0.06	0.75
	ENL G.	*	*	0.09	0.85	0.69	0.74
HGB	OFF	0.37	<0.001	0.68	0.27	0.32	0.56
	ENL F.	0.59	0.07	0.40	0.19	0.13	0.48
	ENL G.	0.08	0.03	0.38	0.46	0.23	0.26
HCT	OFF	0.77	<0.001	0.37	*	*	0.01
	ENL F.	0.50	0.001	0.22	*	*	0.06
	ENL G.	0.19	0.008	0.23	0.19	0.28	0.49
MCV	OFF	0.38	<0.001	0.58	0.98	0.93	0.18
	ENL F.	0.84	<0.001	0.18	0.83	0.84	0.61
	ENL G.	0.45	<0.001	0.19	0.39	0.45	0.49
MCH	OFF	0.38	<0.001	0.84	0.05	0.04	0.43
	ENL F.	*	*	0.08	0.47	0.01	0.38
	ENL G.	0.84	<0.001	0.51	0.99	0.05	0.47
MCHC	OFF	0.24	0.01	0.32	0.03	0.08	0.97
	ENL F.	0.77	0.003	0.59	0.88	0.08	0.63
	ENL G.	0.65	0.73	0.55	0.39	0.60	0.17
PLT	OFF	0.66	0.02	0.56	0.30	0.95	0.99
	ENL F.	0.26	<0.001	0.17	0.24	0.93	0.95
	ENL G.	0.97	0.91	0.71	0.32	0.88	0.58

*P values not relevant due to Exposure by Pack-year interaction term.

Table XVI-3-5

SAMPLE SIZES FOR RANCH HAND OCCUPATION

AND EXPOSURE GROUP ANALYSES

Occupational Category Exposure Category	Officer	Enlisted Flying	Enlisted Ground
Low	111	56	150
Medium	128	58	178
High	125	65	146

In Table XVI-3-4, 2 statistically significant ($P \leq 0.05$) overall exposure group effects are seen and 7 exposure-smoking interaction effects ($P \leq 0.10$) are also present. First, the overall exposure group effects will be described.

The 2 overall exposure group effects occur in the Ranch Hand officer cohort and involve the variables MCH and MCHC. An increasing dose-response relationship is clear in the MCH data, and the high exposure group also has the highest rate of mean corpuscular hemoglobin concentration (MCHC) abnormalities. These findings are suggestive of a herbicide effect, however, similar trends are not noted in the other 2 occupational categories thus decreasing the likelihood of a bonafide herbicide effect by raising the possibility that an unknown confounding variable is operative.

Table XVI-3-6

HEMATOLOGICAL VARIABLE MEAN AND PERCENTS FOR RANCH HAND OCCUPATION-EXPOSURE GROUP ANALYSES

		Adjusted Variable Means			Percent Abnormal**		
Var	Exp Level	OFF	ENL Flying	ENL Ground	Officers	ENL Flying	ENL Ground
RBC	Low	5.11	5.15*	5.23	8.11	8.93	4.00
	Medium	5.07	5.20*	5.34	9.38	8.62	6.74
	High	5.11	5.24*	5.27	8.80	6.45	8.22
WBC	Low	7.03*	8.25	7.63*	11.71	16.07	12.00
	Medium	6.93*	7.91	7.66*	7.03	13.79	14.04
	High	7.15*	7.89	7.81*	10.53	21.54	12.33
HGB	Low	15.82	15.99	16.04	3.60	3.57	4.67
	Medium	15.80	16.11	16.26	2.34	1.72	2.25
	High	15.95	16.19	16.09	0.80	9.23	4.11
HCT	Low	45.36	46.22	46.36	11.71	8.93	8.00
	Medium	45.40	46.42	46.82	10.94	8.62	3.37
	High	45.59	46.84	46.39	11.20	10.77	6.16
MCV	Low	89.02	90.09	88.75	3.60	3.57	2.67
	Medium	89.84	89.53	88.10	3.91	1.72	5.06
	High	89.56	89.70	88.46	4.00	3.08	3.42
MCH	Low	30.94	31.08*	30.61	41.44	46.43	40.67
	Medium	31.14	30.97*	30.50	52.34	44.83	41.01
	High	31.22	30.91*	30.56	58.40	53.85	42.47
MCHC	Low	34.80	34.56	34.54	9.91	8.93	10.67
	Medium	34.73	34.65	34.66	6.25	6.90	6.74
	High	34.94	34.52	34.61	16.00	7.69	9.59
PLT	Low	262.13	294.48	280.94	0.00	3.57	2.67
	Medium	268.20	290.97	282.09	1.56	0.00	0.56
	High	264.09	277.78	282.53	0.00	0.00	1.37

*Unadjusted means given due to smoking (pack-years) by dependent variable interaction.

**All percents given are unadjusted.

The general linear model analysis of the red blood cell count shows an interesting interaction with smoking in Ranch Hand enlisted flying personnel. In the low exposure set of enlisted flying Ranch Handers, smoking cigarettes is associated with increasing RBC values (slope = 0.00562), but the medium exposed and high exposed individuals show decreasing RBC values with smoking (slopes -0.00124 and -0.00457 respectively). This gradient of slopes with exposure is suggestive of a true herbicide effect.

Log-linear analysis of the red blood cell count shows a smoking-exposure interaction among Ranch Hand officers. The data for these officers is given in Table XIV-3-7.

Table XVI-3-7

SMOKING-EXPOSURE INTERACTIONS ON RBC IN RANCH HAND OFFICERS

	% ABNORMAL RBC		
Exposure	Zero Pk-Yrs	1-10 Pk-Yrs	>10 Pk-Yrs
Low	0.00	16.67	13.16
Med	8.51	10.53	9.68
High	9.52	5.88	9.09

This interaction is compatible with an herbicide effect, and reinforces the finding in the enlisted flying personnel.

The WBC count in Ranch Hand officers shows a smoking-exposure interaction ($P < 0.001$). In the low exposure officer set, cigarette use is associated with an increased WBC value (slope = 0.0691), but this association is less in the higher exposure categories (slope in medium exposure category = 0.0251, and slope in the high exposure category is 0.0307). These data suggest that the correlation of leucocyte count to cigarette smoking might be affected by herbicide exposure in Ranch Hand officers. This pattern of decreasing association of leucocyte counts to cigarette smoking with increasing exposure is also suggested by the data for Ranch Hand enlisted ground personnel. In the low exposure set, cigarrette use is also associated with increased WBC values (slope = 0.0466) but this association is least in the high exposed group (slope = 0.0192).

An exposure - pack-year interaction in the HCT data was noted in the officer cohort ($P = 0.01$) and an interaction was also seen in the enlisted flying group. The data describing these interactions is shown in Table XIV-3-8. Relatively smooth dose-response trends are seen in each officer smoking category, but the same regularity is not apparent in the enlisted flying group. It is of interest that the HCT pattern seen in the officer data of Table XIV-3-8 appears to parallel the RBC pattern in the officer data of Table XIV-3-7.

Table XIV-3-8

SMOKING-EXPOSURE INTERACTIONS ON HCT
IN RANCH HAND OFFICERS
AND ENLISTED FLYING PERSONNEL

Occupation	Exposure	% Abnormal HCT Zero Pk-yr	1-10 Pk-yr	>10 Pk-yr
Officers	Low	6.12	16.67	15.79
	Med	8.51	15.79	11.29
	High	23.81	11.76	3.03
Enlisted Flying	Low	37.50	0.00	5.00
	Med	0.00	33.33	5.13
	High	18.18	16.67	7.14

Lastly, a smoking-exposure interaction is seen in the MCH data in the flying enlisted group. In the low exposure group the MCH - pack-year slope is -0.00478, while this slope is positive in the medium and high exposure sets (0.0207 and 0.03083 respectively).

Summary and Conclusions

The ranch hand group has a higher mean corpuscular volume and mean corpuscular hemoglobin than does the comparison group. Also, a dose-response pattern of increasing mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration was found in the Ranch Hand officer cohort. Seven hematologic variable by cigarette use by exposure level interactions were also found. Five of these interactions involved decreasing associations of hematologic measures with smoking with increasing exposure levels. One interaction (for MCH) showed increasing associations with smoking at increased exposure levels, and one interaction was uninterpretable.

These statistical findings display some degree of consistency. However, the statistical differences do not appear to be significant in terms of current medical morbidity.

Chapter XVI-4

PULMONARY FUNCTION AND DISEASE

Bronchitis, cough, dyspnea and acute respiratory irritation and distress have been reported as acute effects following exposure to phenoxy herbicides and dioxin (Berwick, 1970; Bauer et al, 1961; Bashirov, 1969). Little is known about the presence or absence of chronic pulmonary disease following herbicide exposure. These acute effects and the high likelihood of inhalation exposure to herbicide among operation Ranch Hand personnel in Vietnam prompted the evaluation of the pulmonary status of the study participants. In-home questionnaire responses concerning history of pulmonary disease were reviewed to determine the history of reported pulmonary disease in the Ranch Hand and comparison groups. The analysis of past pulmonary disease included data from the total comparison group. All other analyses in this subchapter were performed on all Ranch Hand individuals (1045) and the subset of original comparisons (773) who participated in the physical examination, except for a few individuals omitted due to missing pulmonary function data. Table XVI-4-1 presents the distribution of reported pulmonary disease in the Ranch Hand group, the entire comparison group, and in the subset of original comparisons.

Table XVI-4-1

DISTRIBUTION OF REPORTED PULMONARY DISEASE IN THE RANCH HAND AND COMPARISON GROUPS

	Group		
Diagnosis (ICD-9 Code)	Original Comparison	Ranch Hand	Total Comparison
Tuberculosis and fungal infection (010-018; 114-116)	9	11	10
Pneumonia and Acute infections (480-487; 460-466)	10	6	11
Neoplasia (160-165; 212)	1	3	2
Chronic sinusitis and other upper respiratory disease (470-478; 480-519)	426	689	687
	P=0.20 (Original Comparison vs. Ranch Hand)		P=0.63 (Ranch Hand vs. Total Comparison)

The distribution of reported disease is not significantly different between the Ranch Hand group and either the original comparisons or the entire comparison group.

Two measures of pulmonary function obtained during the physical examination and a third variable, derived from the other two, were analyzed. The forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) were determined. Prior to being analyzed, these two quantities were expressed as a percent of the predicted values for healthy, nonsmoking males (Morris et al, 1971). The third variable analyzed was the derived ratio of FEV_1 to FVC. Group differences were tested using both an unadjusted one-way analysis of variance and an analysis of covariance adjusting for age and smoking habits. The results of the analysis of the unadjusted mean values for the FVC, FEV_1 and the FEV_1/FVC ratio are presented in Table XVI-4-2.

Table XVI-4-2

ANALYSIS OF THE UNADJUSTED MEANS OF
PULMONARY FUNCTION PARAMETER

Parameter	Group	N	Mean	Std. Dev.	P Value
FVC	Ranch Hand	1033	98.87%	13.15	0.97
(%Predicted)	Comparison	761	98.84%	12.98	
FEV_1	Ranch Hand	1033	105.58%	15.65	0.69
(% Predicted)	Comparison	761	105.87%	15.36	
FEV_1/FVC	Ranch Hand	1035	0.8031%	0.0663	0.87
	Comparison	764	0.8026%	0.0670	

There are no significant unadjusted group differences between the Ranch Hand and comparison group. However, there were statistically significant interactions between age, group and pulmonary function in the analysis of both FVC and FEV_1 ($P = 0.04$ and 0.01 respectively). Similarly, smoking habits interacted significantly with the FEV/FVC ratio ($P = 0.03$). As a result, fully adjusted testing was considered to be inappropriate. However, comparison of the regression planes using the mean values of the covariables revealed P values of 0.86, 0.79, and 0.85 respectively for the FVC, FEV_1 and FEV_1/FVC ratio. These values are observed to be quite similar to those seen in the unadjusted analyses.

An analysis of variance of the unadjusted means for low, medium, and high exposure among the Ranch Hand group was conducted in each occupational category. These analyses revealed no consistent association between exposure level and pulmonary function. The results are presented in Table XVI-4-3. The only significant findings were in the FEV_1/FVC ratio in the enlisted categories. However, these findings were inconsistent, with the lowest exposed individuals in the enlisted flying category having the lowest mean ratio (percent performance) and higher exposed individuals doing better. In the enlisted ground personnel the mean ratio was lowest in the most heavily exposed group. Thus, while statistically significant, these findings do not conform to classic dose-response relationships.

Table XVI-4-3

HERBICIDE EXPOSURE ANALYSIS OF PULMONARY FUNCTION PARAMETERS, UNADJUSTED FOR COVARIATES OF AGE AND SMOKING

Occupational Category	Parameter	Exposure Level	N	Mean	Std Dev	P Value
Officer	FVC (% Predicted)	Low	110	100.81	12.80	
		Medium	128	99.61	13.53	0.55
		High	125	101.40	12.96	
	FEV_1 (% Predicted)	Low	110	108.17	15.46	
		Medium	128	107.27	16.37	0.69
		High	125	108.94	14.46	
	FEV_1/FVC	Low	110	0.799	0.067	
		Medium	128	0.792	0.062	0.64
		High	125	0.798	0.056	
Enlisted Flying	FVC	Low	56	99.84	14.19	
		Medium	57	95.78	11.88	0.24
		High	65	96.68	14.12	
	FEV_1	Low	56	102.75	17.36	
		Medium	57	104.13	14.52	0.90
		High	65	103.80	16.89	
	FEV_1/FVC	Low	56	0.768	0.070	
		Medium	58	0.819	0.106	0.003
		High	65	0.803	0.063	
Enlisted Ground	FVC	Low	150	98.22	12.17	
		Medium	178	98.44	13.88	0.87
		High	145	97.70	11.97	
	FEV_1	Low	150	105.60	14.54	
		Medium	178	105.00	15.42	0.16
		High	145	102.47	14.85	
	FEV_1/FVC	Low	150	0.817	0.056	
		Medium	178	0.819	0.058	0.0005
		High	146	0.794	0.068	

Analyses of covariance adjusting for age and smoking were possible in some of the occupational categories, and the results of these analyses are presented in Table XVI-4-4.

Table XVI-4-4

ANALYSES OF PULMONARY FUNCTION AND HERBICIDE EXPOSURE, ADJUSTED FOR SMOKING AND AGE

Occupational Category	Parameter	P Value for the Exposure Analysis
Officer	FVC	0.26
	FEV_1	0.28
	FEV_1/FVC	0.68
Enlisted Flying	FVC	0.13*
	FEV_1	0.90*
	FEV_1/FVC	0.004
Enlisted Ground	FVC	0.62
	FEV_1	0.47
	FEV_1/FVC	0.03*

*= Significant covariable interaction

These adjusted analyses identified significant associations in the FEV_1/FVC ratio in both enlisted categories. However, there was significant interaction between exposure level, the FEV_1/FVC ratio, smoking habits and age in the enlisted ground category. As noted in Table XVI-4-4, there was also interaction in the enlisted flying category for both FVC and FEV_1. When the regression planes were compared using the mean values of the age and smoking covariables, the resultant P values were as follows: Enlisted flying, FVC $P = 0.10$; Enlisted flying FEV_1 $P = 0.98$; Enlisted ground FEV_1/FVC $P = 0.02$. These P values are essentially the same as those observed in the interactions. They are also similar to those seen in the unadjusted analyses. As noted in the unadjusted analysis in Table XVI-4-3 the pattern did not suggest a consistent dose response.

Summary

In a few instances the results of the statistical analyses revealed significant ($P \leq 0.05$) or suggestive ($P = 0.10$ to 0.20) differences in pulmonary function. There were no differences detected between the Ranch Hand and comparison groups. Where significant differences were noted in the exposure index analyses, they were isolated and inconsistent in character. There were differences in the age by smoking by exposure interaction in the two groups, but it is not possible to characterize these further at this time. It may be possible to clarify these differences during follow-up phases of the study. In summary, there is no indication in the baseline physical examination that exposure to herbicide in Vietnam adversely affected pulmonary function as measured 10 to 20 years after the exposure.

Chapter XVI-5

RENAL DISEASE AND FUNCTION

1. Introduction

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

2. Laboratory Test Results

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

Table XVI-5-1

URINARY OCCULT BLOOD AND PROTEIN RESULTS
BY GROUP MEMBERSHIP

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

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

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

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

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

Table XVI-5-2

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

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

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

Urine creatinine clearance levels were determined by the formula:

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

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

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

Table XVI-5-3

MEAN VALUES OF CREATININE CLEARANCE BY GROUP,
UNADJUSTED FOR COVARIATES

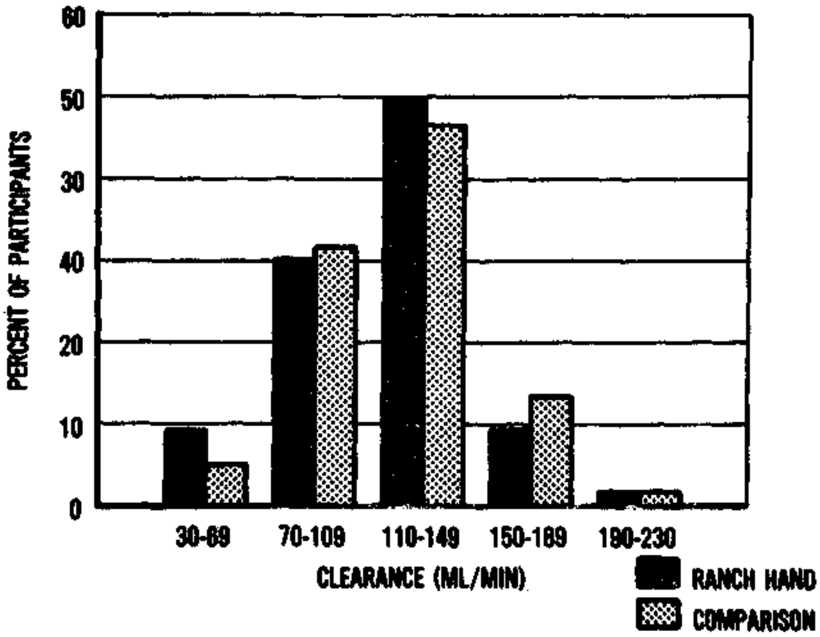
Group	Number	Mean (ml/min)	Standard Deviation
Comparison	439	119.43	30.70
Ranch Hand	628	116.60	31.26

P = 0.142

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

Figure XVI-5-1

CREATININE CLEARANCE FREQUENCY DISTRIBUTION BY GROUP



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

3. Questionnaire Versus Laboratory Results

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

Table XVI-5-4

HISTORY OF KIDNEY DISEASE BY GROUP

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

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

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

Table XVI-5-5

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

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

P = 0.94 (History by abnormality interaction)

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

4. Herbicide Exposure Analyses

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

Table XVI-5-6

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

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

P = 0.0504

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

5. Summary

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

Chapter XVI-6

ENDOCRINE FUNCTION

1. Introduction

TCDD is known to produce a broad spectrum of metabolic phenomena in animal experimental subjects treated with sufficiently large doses. The pattern of effects is quite complex. Hypothyroxinemia has been produced in rats (Potter et al, 1983), and this may be associated with increased biliary elimination of thyroxine (Bastomsky, 1977). Hypoglycemia has been produced in rats (Gasiewicz et al, 1980, Potter et al, 1983) at the same time that serum and pancreatic insulin levels fell (Potter et al, 1983). TCDD has been observed to reduce hepatic catabolism of testosterone in the rat (Nienstedt et al, 1979).

Based on animal data, the physical examination in this study obtained data for thyroid function (T3 uptake, serum T4 and the free thyroxine index or FTI), glucose metabolism (blood glucose level taken 2 hours after a standard carbohydrate load) and serum testosterone level. These 5 variables are listed in Table XVI-6-1 together with a description of normal and abnormal levels provided by the Kelsey-Seybold contract effort.

Table XVI-6-1

FIVE ENDOCRINOLOGICAL VARIABLES
AND THEIR NORMAL AND ABNORMAL LEVELS

Variable Name	Variable Abbreviation	Abnormal (Low)	Normal Range	Abnormal (High)
T3 Uptake	T3	<27%	27%-37%	>37%
Serum T4	T4	<4.7 μg/dl	4.7-12.5 μg/dl	>12.5 μg/dl
Free Thyroxine Index	FTI	<1.3	1.3-4.6	>4.6
2 Hour Post-prandial Glucose	GLU 2 HR	NA	<120 mg/dl	≥120 mg/dl
Serum Testosterone	TEST	<400 ng/dl	400-1200 ng/dl	>1200 ng/dl

Each study subject was asked to follow a standardized diet prior to arrival at the examination site. Not all participants complied with the diet. Table XVI-6-2 shows dietary compliance by group.

Table XVI-6-2

DIETARY COMPLIANCE BY GROUP

Group	Complied with Diet	Did Not Comply With Diet	Dietary Compliance Unknown
Ranch Hand	896 (86%)	96	53
Comparison	676 (87%)	70	27

The groups are not different as regards dietary compliance (P = 0.262). Also dietary compliance was not found to be associated with the likelihood of being in the high abnormal GLU 2 HR category. Thus, in Tables XVI-6-3 and XVI-6-5 participants were used irrespective of dietary compliance status.

2. Data Analysis

Table XVI-6-3 shows unadjusted percentages of the 5 endocrinological variables by variable level and group. (For this table and all other analyses in this chapter, all Ranch Hand participants (N = 1045) and all original controls (N = 773) were used as the basic data set). In the analysis of thyroid hormones, data from individuals with thyroidectomies were removed (7 Ranch Handers and 3 original comparisons), and in the analysis of testosterone, data from individuals with orchiectomies (5 Ranch Handers and 1 original comparison) were removed. Other denominator variations occurred due to missing covariates.

A group difference in T3 uptake is noted in Table XVI-6-3. The Ranch Hand group has fewer individuals in the low category and more individuals in the high category than does the comparison group. The same directionality is noted with the T4 and FTI variables. No group differences are found in GLU 2 HR or TEST.

Since hormone levels can be correlated with age and physical habitus, an analysis of the 5 endocrinological variables was attempted adjusting for age in years (dichotomized as less than or equal to 40 years and greater than 40 years) and for percent body fat (trichotomized as less than 10%, 10-25%, greater than 25%). There are too few abnormalities for a full analysis of any of the 5 endocrinological variables. However, for T3 and TEST, analyses could be performed on those individuals with 10% body fat or greater and having low abnormal or normal dependent variable values. Similarly, an analysis of GLU 2 HR values was possible on those individuals with 10% body fat or greater. The data for these 3 adjusted analyses are presented in Tables XVI-6-4, XVI-6-5 and XVI-6-6. Log-linear models were used in these analyses.

Table XVI-6-3

UNADJUSTED PERCENTAGES FOR FIVE ENDOCRINOLOGICAL VARIABLES BY VARIABLE LEVEL AND GROUP

Variable	Group	N	Low	Normal	High	P Value For Group Difference
			Variable Level			
T3	RH	1032	5.72%	93.41%	0.87%	0.020
	COM	767	8.47%	91.26%	0.26%	
T4	RH	1033	0.10%	99.13%	0.77%	0.250
	COM	767	0.39%	99.22%	0.39%	
FTI	RH	1033	0.00%	99.71%	0.29%	0.085
	COM	767	0.26%	99.74%	0.00%	
GLU 2 HR	RH	1040	NA	84.81%	15.19%	0.234
	COM	770	NA	82.73%	17.27%	
TEST	RH	1034	4.93%	94.58%	0.48%	0.414
	COM	769	6.37%	93.11%	0.52%	

Table XVI-6-4 shows a group difference in T3 uptake which is age specific (P = 0.005). There are more low T3 values in the comparison group than in the Ranch Hand group in the 40 and under-40 age group, but the groups are similar above 40 years of age. A highly statistically significant association of T3 hypothyroxinemia with body fat is noted within the groups (P = 0.004).

Table XVI-6-5 shows no group difference in the observed proportions of hyperglycemia ($\geq$ 120 mg/dl). Age and body fat are seen to influence these proportions (P < 0.001 in both instances), and the effect is about the same in both groups.

Table XVI-6-6 shows no group difference in the observed proportions of low testosterone. Age and body fat both influence these proportions (P = 0.022 for age and P < 0.001 for body fat), and the effect is approximately the same in both groups.

Using the categories for normal and abnormal levels shown in Table XVI-6-1, it was not possible to meaningfully carry out an exposure index analysis of the 5 endocrinological variables, due to sample size limitations.

Table XVI-6-4

PERCENT OF ABNORMALLY LOW T3 VALUES
BY GROUP, AGE AND BODY FAT CATEGORY*

Age	Group	% T3 Low Abnormal in 10-25% Body Fat Subgroup		% T3 Low Abnormal in > 25% Body Fat Subgroup	
≤40	RH	2.59	(9/347)	6.58	(5/76)
≤40	COM	7.89	(18/228)	19.15	(9/47)
>40	RH	6.49	(30/462)	10.94	(14/128
>40	COM	7.43	(28/377)	9.26	(10/108)

* Abnormally high individuals and lean individuals (less than 10% body fat) were removed from the analysis due to sample size limitations.

Table XVI-6-5

PERCENT ABNORMAL GLU 2 HR VALUES
BY GROUP, AGE AND BODY FAT CATEGORY*

Age	Group	% GLU 2 HR in Abnormal Category in 10-25% Body Fat Subgroup		% GLU 2 HR in Abnormal Category in >25% Body Fat Subgroup	
≤40	RH	6.25	(22/352)	17.11	(13/76)
≤40	COM	6.55	(15/229)	17.02	(8/47)
>40	RH	18.01	(85/472)	28.46	(37/130)
>40	COM	18.25	(69/378)	36.36	(40/110)

* Lean individuals (less than 10% body fat) were removed from the analysis due to sample size limitations.

Table XVI-6-6

PERCENT ABNORMAL LOW TESTOSTERONE VALUES
BY GROUP, AGE AND BODY FAT CATEGORY*

Age	Group	% Testosterone Low Abnormal in 10-25% Body Fat Subgroup		% Testosterone Low Abnormal in > 25% Body Fat Subgroup	
≤40	RH	2.00	(7/350)	7.89	(6/76)
≤40	COM	3.52	(8/227)	10.64	(5/47)
>40	RH	3.46	(16/463)	16.15	(21/130
>40	COM	4.00	(15/375)	19.09	(21/110)

* Abnormally high individuals and lean individuals (less than 10% body fat) were removed from the analysis due to sample size limitations.

Analysis of covariance is less vulnerable to the data limitations of sparse or empty cells than are log-linear models. Thus, the Ranch Hand group was contrasted with the comparison group in terms of the 5 endocrinological variables using analysis of covariance adjusting for age and percent body fat. In these analyses, all variables except group indicators were used as continuous variables. In the analysis of thyroid hormones, data from individuals with thyroidectomies were removed, and in the analysis of testosterone levels, individuals with orchiectomies were removed. In the analysis of glucose levels, all participant data were used irrespective of dietary compliance as compliance was not found to influence glucose levels.

Table XVI-6-7 provides unadjusted and adjusted means. When a group-by-age or group-by-body fat interaction was observed with $P < 0.10$, adjusted means, and age and body fat main effects are not reported.

One overall group difference is noted in Table XVI-6-7. Specifically, the Ranch Handers show a higher testosterone level than do comparison participants ($P = 0.02$ unadjusted, 0.06 adjusted). Both increasing age and increasing body fat were found to be associated with decreasing testosterone level with slopes being -3.8 ng/dl per year of life and -12.6 ng/dl per % body fat.

Table XVI-6-7

RANCH HAND - COMPARISON GROUP MEANS OF ENDOCRINE VARIABLES

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Means	Adj'd Mean	P Value for Adj'd Means	Remarks about Adjusting Covariates
T3	Com	770	30.14	0.21	*	*	Group-by-age interaction
Uptake (%)	RH	1037	30.28				(P = 0.026)
T4	Com	770	8.39	0.31	8.39	0.38	None significant at P<.05
(μg/dl)	RH	1038	8.46		8.45		
FTI	Com	770	2.51	0.07	2.51	0.13	Age (P<.001)
	RH	1038	2.54		2.54		% Body fat (P<.001)
GLU 2HR	Com	773	102	0.37	*	*	Group-by-age interaction
(mg/dl)	RH	1045	104				(P=.006)
TEST	Com	772	634	0.02	637	0.06	Age (P<.001)
(ng/dl)	RH	1039	654		652		% Body fat (P<.001)

Two other group differences are noted in Table XVI-6-7; however, these are associated with group-by-age interactions. In both the Ranch Hand and comparison groups, decreasing T3 uptake is observed associated with advancing age, but the slope was found to be -0.0068% per year in the comparison group while it is -0.0495% per year in the Ranch Hand group. Glucose levels, measured 2 hours into the glucose tolerance test, were observed to increase with age in both the comparison and Ranch Hand group; however, the rate of increase is 0.77 mg/dl per year in the comparison group and 1.53 mg/dl per year in the Ranch Hand group.

Dose-response data within the Ranch Hand group are provided in Tables XVI-6-8, XVI-6-9 and XVI-6-10. No overall statistically significant dose-response relationships were detected; however, 5 exposure group by covariate interactions were noted. These interactions are summarized in Table XVI-6-11. No interactions are seen with respect to the variables T3 or T4.

Table XVI-6-8

RANCH HAND OFFICERS
ENDOCRINE DOSE-RESPONSE DATA

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Mean	Adj'd Mean	P Value for Adj'd Mean	Remarks about Adjusting Covariates
T3	L	110	30.9	0.39	30.8	0.88	Age (P=0.033)
	M	126	30.6		30.7		% Body fat (P=0.039)
	H	125	30.6		30.6		
T4	L	110	8.21	0.12	8.23	0.89	None
	M	126	8.15		8.15		
	H	125	8.22		8.22		
FTI	L	110	2.51	0.59	*	*	Age-exposure interaction (P=0.042)
	M	126	2.47				
	H	125	2.49				
GLU 2 HR	L	111	106.7	0.90	*	*	% Body fat-exposure interaction (P=0.041)
	M	128	104.2				
	H	125	106.8				
TEST	L	111	614.8	0.85	*	*	% Body fat-exposure interaction (P=0.011)
	M	127	614.2				
	H	123	604.5				

Table XVI-6-9

RANCH HAND - FLYING ENLISTED PERSONNEL
ENDOCRINE DOSE-RESPONSE DATA

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Mean	Adj'd Mean	P Value for Adj'd Mean	Remarks about Adjusting Covariates
T3	L	59	29.6	0.57	29.6	0.59	None
	M	59	30.0		30.0		
	H	64	30.0		30.1		
T4	L	59	8.85	0.32	8.85	0.32	None
	M	59	8.48		8.49		
	H	64	8.48		8.50		
FTI	L	59	2.60	0.45	*	*	% Body fat-exposure interaction (P=0.03)
	M	59	2.51				
	H	64	2.60				
GLU 2 HR	L	59	102.3	0.88	102.3	0.78	Age (P=0.01)
	M	59	105.9		108.0		
	H	66	105.6		103.8		
TEST	L	59	663.5	0.98	659.8	0.90	% Body fat (P<0.001)
	M	58	657.8		653.5		
	H	66	658.5		666.7		

Table XVI-6-10

RANCH HAND - GROUND ENLISTED PERSONNEL
ENDOCRINE DOSE-RESPONSE DATA

Variable	Group	N	Unadj'd Mean	P Value for Unadj'd Mean	Adj'd Mean	P Value for Adj'd Mean	Remarks about Adjusting Covariates
T3	L	151	29.8	0.30	29.9	0.18	Age (P<0.001)
	M	176	30.2		30.1		% Body fat (P<0.003)
	H	148	30.3		30.4		
T4	L	151	8.58	0.89	8.59	0.89	None
	M	177	8.67		8.67		
	H	148	8.59		8.58		
FTI	L	151	2.55	0.69	2.55	0.53	Age (P=0.01)
	M	177	2.58		2.56		% Body fat (P=0.03)
	H	148	2.60		2.61		
GLU 2 HR	L	151	99.9	0.60	*	*	% Body fat-exposure interaction (P=0.09)
	M	179	104.8				
	H	148	103.7				
TEST	L	151	686.4	0.97	685.6	0.93	Age (P=0.02)
	M	179	680.5		678.2		% Body fat (P<0.001)
	H	146	683.0		684.4		

Table XVI-6-11

ENDOCRINE DOSE - COVARIATE INTERACTIONS

	T3	T4	FTI	GLU 2 Hr	TEST
Ranch Hand Officers	No interactions	No interactions	Age-exposure interaction (P=0.042)	% Body fat-exposure interaction (P=0.041)	% Body fat-exposure interaction (P=0.011)
Ranch Hand Flying Enlisted	No interactions	No interactions	% Body fat-exposure interaction (P=0.03)	No interaction	No interactions
Ranch Hand Ground Enlisted	No interactions	No interactions	No interactions	% Body fat-exposure interaction (P=0.09)	No interactions

The FTI shows an age-exposure interaction among the officers and a % body fat-exposure interaction in the flying enlisted Ranch Hand group. Among the officers, FTI increased by 0.0041 per year of life in the low exposure group but decreased by 0.0127 and 0.0079 per year in the medium and high exposure groups respectively. No effect of body fat was suggested by the officer data. Among the flying enlisted, FTI did not appear affected by age, but increased with increasing % body fat in the low and medium exposure groups (0.00295 and 0.00378 per % body fat respectively) while it decreased with body fat (-0.0241 per % body fat) in the high exposure group. These FTI effects are interesting; however, the lack of consistency between occupational and exposure categories leads to doubt that an actual herbicide effect exists.

Both Ranch Hand officers and ground enlisted personnel show comparable body fat-exposure interactions affecting glucose levels. The glucose level-body fat slopes are given in Table XVI-6-12. In both the officer and ground enlisted categories, the low exposed individuals show a decreasing blood glucose with increasing % body fat, but this relationship changes to a positive correlation in the medium and high exposure categories.

Table XVI-6-12

CHANGE IN GLUCOSE LEVEL PER % BODY FAT
(mg/dl PER % BODY FAT)
BY HERBICIDE EXPOSURE LEVEL IN TWO RANCH HAND GROUPS

Exposure Category	Ranch Hand Officers	Ranch Hand Ground Enlisted
Low	+1.18	-0.30
Medium	+2.94	+1.75
High	+1.26	+1.36

A % body fat by exposure interaction is also observed to affect testosterone levels in Ranch Hand officers with a very low probability that the effect could be due to chance (P = 0.011). Low exposed officers show a decrease in serum testosterone levels of 4.5 ng/dl per % body fat while medium and high exposed officers show decreases of 16.6 ng/dl and 15.3 ng/dl per % body fat respectively.

3. Summary

The Ranch Hand group was found to differ from the comparison group with respect to proportions of individuals in normal and abnormal thyroid hormone categories. The difference is a tendency toward hyperthyroxinemia which is directionally opposite to what would be expected on the basis of subacute animal studies. On the other hand, decreasing T3 uptakes are associated with advancing age in both groups with the slope being much steeper in the Ranch Hand group. Finally, no meaningful association of thyroid hormone levels with the exposure index were found. Thus, in sum, no definite herbicide effect on thyroid function can be considered demonstrated; however, it also cannot be confidently asserted that a herbicide effect on thyroid function has not occurred. As a group, Ranch Hand personnel have higher testosterone levels than comparison individuals and Ranch Hand officers evidence a decrease in testosterone level with increasing body fat that is related to herbicide exposure category (higher exposures are associated with greater decreases in testosterone with body fat). Since subacute animal studies have shown decreased catabolism of testosterone, higher serum levels could be expected. Thus, this finding in the present study may reflect an herbicide effect, whose long-term impact will require further clinical evaluation.

Overall, Ranch Hand blood glucose levels are not statistically significantly different from those of comparison individuals. However, positive associations of glucose levels with age are greater in the Ranch Hand group than in the comparison group, and in both the Ranch Hand officer and ground enlisted groups significant exposure - body fat interactions exist on glucose levels. Thus, a subtle toxicological effect of herbicide on glucose metabolism may have been detected. It will be important and interesting to follow these groups in time with respect to the incidence of diabetes.

Chapter XVII

INDIVIDUAL HEALTH ASSESSMENT

1. Personal Habits and Characteristics

The personal characteristics of the Ranch Hand and comparison individuals were obtained from the in-home questionnaire. The areas of tobacco, alcohol, and marijuana use, personal and family income, education, religion, active duty, retired/separated status, and risk-taking behavior received particular attention. The number of Ranch Hand and comparison group individuals reporting a listing of past traumatic injuries, poisonings, and/or toxic effects (ICD-9-CM Codes 960-999) were also determined.

The smoking and alcohol use habits of the study subjects are displayed in Table XVII-1.

Table XVII-1
HISTORY OF TOBACCO AND ALCOHOL USE AMONG THE STUDY PARTICIPANTS

	Group					
	Original Comparisons		Ranch Hand		All Comparisons	
Habit	Yes (%)	No	Yes (%)	No	Yes (%)	No
Current Use of Cigarettes	313 (40.5%)	459	478 (45.7%)	567	484 (39.6%)	739
		P = 0.03			P = 0.003	
Past History of Cigarettes	552 (72.3%)	212	758 (73.2%)	278	861 (71.1%)	350
		P = 0.67			P = 0.28	
Past History of Cigar Use	92 (11.9%)	680	99 (9.5%)	942	141 (11.5%)	1081
		P = 0.10			P = 0.12	
Past History of Pipe Use	157 (20.4%)	613	200 (19.4%)	829	246 (20.2%)	970
		P = 0.62			P = 0.64	
Past History of Marijuana Use	22 (2.8%)	750	53 (5.1%)	992	62 (5.1%)	1160
		P = 0.02			P = 1.00	
Current Use of Alcohol	447 (58.6%)	316	609 (58.9%)	425	694 (57.3%)	518
		P = 0.89			P = 0.43	
Past History of Alcohol Use	478 (63.0%)	281	635 (62.2%)	386	773 (64.7%)	421
		P = 0.74			P = 0.21	

The mean number of cigarettes currently smoked and the mean number of alcohol-containing drinks consumed per day by those currently reporting use of these substances were determined. Similarly, the mean pack-years, cigar-years, pipe-years, drink-years and marijuana joint-years were determined for the groups in the study. These data are presented in Table XVII-2.

Table XVII-2

MEAN USE OF TOBACCO PRODUCTS AND ALCOHOL
IN THOSE REPORTING USE OF THESE SUBSTANCES

	Mean Usage Level					
	Original Comparisons		Ranch Hand		All Comparisons	
Substance	Mean	(Median)	Mean	(Median)	Mean	(Median)
Cigarettes per day (current use)	28.28	(30)	27.21	(25)	27.72	(30)
Cigarette pack-years (cumulative)	23.47	(20.12)	23.89	(20.91)	22.92	(19.58)
Cigar-years (cumulative)	21.26	(8.11)	19.12	(9.38)	20.80	(7.33)
Pipe-years (cumulative)	26.96	(6)	26.32	(7.23)	26.26	(5.71)
Marijuana Joint-years (cumulative)	7.60	(2.52)	7.12	(3.54)	8.26	(2.88)
Alcohol drinks per day (current use)	2.33	(2)	2.35	(2)	2.38	(2)
Drink-years (cumulative)	36.48	(26.31)	40.48	(24.23)	34.87	(25.08)

In most of the cumulative measurements (e.g., pack-years) the median level of use was lower than the mean level, indicating that the heavy users of these substances skewed the distributions. However, in the measurements of current use, there was little evidence for this effect.

The median income levels of the Ranch Handers and the original comparison were the same with personal income ranging from $20,000 - $24,999 and total family income ranging from $30,000 - $34,999. The median personal income of the entire comparison group was also in the $20,000 - $24,999 range, but the median family income remained in this same category.

The educational backgrounds of the groups were not significantly different. Religious preferences of the groups were also similar. These data are shown in Tables XVII-3 and XVII-4.

Table XVII-3

EDUCATIONAL BACKGROUND BY GROUP

	Group					
	Original Comparisons		Ranch Hand		All Comparisons	
Educational Level	Number	(%)	Number	(%)	Number	(%)
High School/GED	430	(55.63)	580	(55.50)	661	(54.01)
Associate Degree	53	(6.86)	67	(6.41)	96	(7.84)
BA/BS Degree	152	(19.66)	197	(18.85)	249	(20.34)
Graduate Degree	132	(17.07)	187	(17.89)	206	(16.83)
Unknown	6	(0.78)	14	(1.34)	12	(0.98)

P = 0.78 (Original Comparisons vs. Ranch Hand) P = 0.48 (Ranch Hand vs. All Comparisons)

Table XVII-4

RELIGIOUS PREFERENCE BY GROUP

Religion	Group: Original Comparisons Number	(%)	Ranch Hand Number	(%)	All Comparisons Number	(%)
Protestant	699	(66.89)	531	(68.69)	816	(66.68)
Catholic	218	(20.86)	162	(20.96)	263	(21.49)
Jewish	9	(0.86)	12	(1.55)	16	(1.31)
Other	34	(3.25)	20	(2.59)	49	(4.00)
None	85	(8.13)	48	(6.21)	80	(6.54)

P = 0.29 (Original Comparisons vs. Ranch Hand)   P = 0.50 (Ranch Hand vs. All Comparisons)

The current military status of each individual was determined as either active duty, retired, separated, reserve status, or deceased, and there were no statistically significant differences between the Ranch Handers and the subset of original comparisons (P = 0.23); however, there was a significant difference (P = 0.01) between the Ranch Handers and the total comparison group. These data are presented in Table XVII-5.

Table XVII-5

MILITARY STATUS BY GROUP

Military Status	Group: Original Comparisons Number	(%)	Ranch Hand Number	(%)	All Comparisons Number	(%)
Active Duty	113	(14.64)	153	(14.66)	184	(16.74)
Retired	420	(54.40)	515	(49.33)	593	(53.96)
Separated	196	(25.39)	305	(29.21)	247	(22.47)
Reserve Forces	39	(5.05)	64	(6.13)	69	(6.28)
Deceased*	4	(0.52)	7	(0.67)	6	(0.55)

P = 0.23 (Original Comparisons vs. Ranch Hand)   P = 0.01 (Ranch Hand vs. All Comparisons)

*Deceased subsequent to the physical examination.

Risk-taking behavior patterns were assessed by a series of questions (i.e., "Have you participated three or more times in ....activity?") that emphasized participation in potentially dangerous recreational activities. These data are tabulated in Table XVII-6.

Table XVII-6

RISK-TAKING BEHAVIOR BY GROUP

Activity	Original Comparisons Yes (%)	Original Comparisons No	Ranch Hand Yes (%)	Ranch Hand No	All Comparisons Yes (%)	All Comparisons No
Scuba Diving	88 (11.40)	684	103 (9.87)	941	155 (12.68)	1067
	P = 0.29				P = 0.04	
Auto, Boat or Motorcycle Racing	77 (9.97)	695	132 (12.64)	912	140 (11.46)	1082
	P = 0.08				P = 0.39	
Aerobatic Flying	25 (3.24)	747	29 (2.78)	1015	39 (3.19)	1183
	P = 0.57				P = 0.57	
Sky Diving	12 (1.55)	760	14 (1.34)	1030	29 (2.37)	1193
	P = 0.71				P = 0.07	
Hang Gliding	4 (0.52)	768	6 (0.57)	1038	13 (1.06)	1209
	P = 0.87				P = 0.20	
Mountain Climbing	35 (4.53)	737	61 (5.84)	983	63 (5.16)	1159
	P = 0.22				P = 0.47	
One or More Risk-taking activities	172 (22.3)	601	253 (24.2)	792	308 (25.2)	916
	P = 0.33				P = 0.60	

Only in motor vehicle racing (automobile, boats and motorcycles) was there a borderline suggestion of a difference in risk-taking behavior between the Ranch Handers and the original comparison subset. In contrast, there was a statistically significant difference between the Ranch Handers and the entire comparison group in scuba diving (P = 0.04) and a borderline difference (P = 0.07) in sky diving. In both of these instances, the comparisons had higher rates of participation. In combining all activities, there was no significant difference in risk-taking behavior between the Ranch Handers and the original or entire comparison group.

Table XVII-7 contains the distribution of reported past injuries and poisonings by ICD code for each group. Conditional unadjusted chi-square testing reveals no significant group differences in these distributions.

Table XVII-7

DISTRIBUTION OF REPORTED INJURIES AND POISONINGS BY GROUP

Injury (ICD Code)	Group: Original Comparisons	Group: Ranch Hand	Group: All Comparisons
Fractures, Dislocations, Sprains (800-848)	11	11	17
Intracranial, chest; abdominal and pelvic injuries; open wounds; nerve and spinal cord injuries (850-897; 925-929; 950-957)	3	4	8
Late effects; superficial injuries and contusions; burns (905-924; 940-949)	5	2	6
Traumatic complications (958-959)	5	9	8
Poisonings, toxic effects; other specified causes (960-989)	3	0	4

P = 0.23 (Original Comparisons vs. Ranch Hand)   P = 0.31 (Ranch Hand vs. All Comparisons)

2. Health Abnormalities Detected at Physical Examination

Throughout previous chapters, health of the participants has been assessed in a variety of interrelated ways. Normal-abnormal categorizations, or continuously distributed clinical variables have been defined organ system by isolated organ system, categorized into physical, mental, reproductive, biochemical, and machine-results parameters, all of which were qualified by overall historic and diagnostic impressions. This research approach has not been suitable to assess total individual health. Since such a task would involve complete listings of all past abnormalities and current normalities-abnormalities by individual, these citations would exceed the scope of this report. This chapter section attempts to assess the overall health of individuals in three ways: the summation of abnormalities of major components of each of the 12 organ systems; the summation of a weighted score of the same abnormalities; and a summary count of medical codes for historical disease and disease suspected/detected at the physical examination.

a. Summation of Individual Abnormalities

In 8 of the 12 clinical areas, virtually all individuals were found to have complete examination data, and all of the selected parameters of individual health could be evaluated. Table XVII-8 provides the number of Ranch Hand and original comparison group individuals with incomplete data who were not included in the tabulation for each organ system.

Table XVII-8

DISTRIBUTION OF INDIVIDUALS WITH INCOMPLETE DATA
OMITTED FROM ANALYSIS OF INDIVIDUAL HEALTH

Organ System	Ranch Hand	Comparison
General Health	8	6
Malignancy	0	0
Reproductive	473	352
Neurological	31	19
Psychological	4	0
Hepatic	0	0
Dermatology	0	0
Cardiovascular	4	3
Hematologic	0	0
Pulmonary	5	3
Renal	0	0
Endocrine	9	3

The assessment of the reproductive system is based solely on the sperm count. Those individuals noncompliant for the collection of semen or those having had vasectomies or orchiectomies were excluded from this analysis. In the psychologic, hepatic and neurologic clinical areas, there were sufficient numbers of individuals with missing data to warrant separate analyses of individuals with complete data and individuals with partial data. The data and results of the analysis of abnormalities by organ system are presented in Table XVII-9. As noted for the psychologic, neurologic and hepatic data, subset analyses were accomplished.

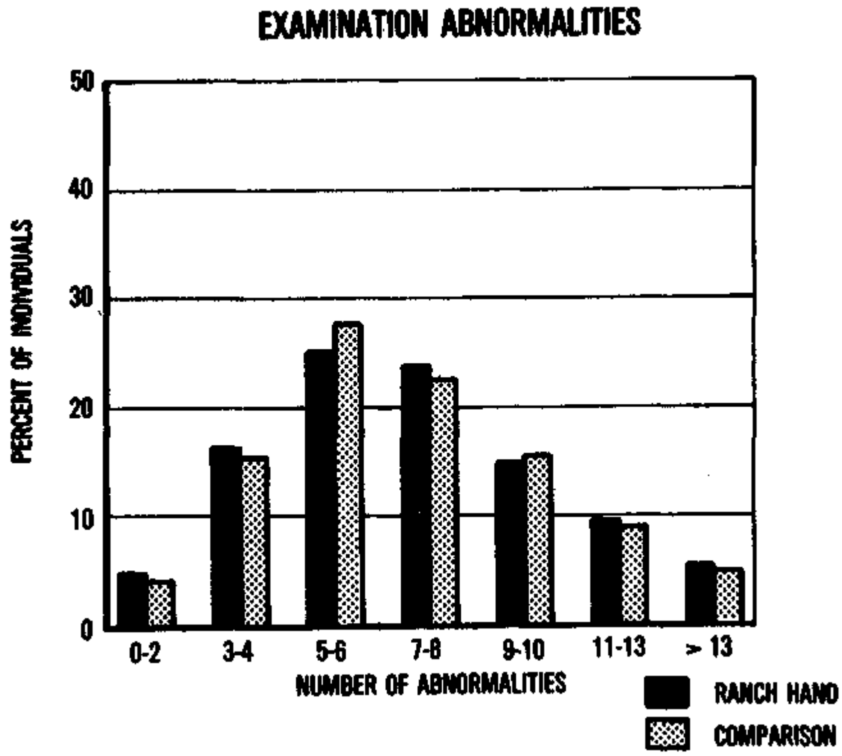
Table XVII-9

COUNT DATA
NUMBER OF HEALTH ABNORMALITIES BY ORGAN SYSTEM AND GROUP
(UNADJUSTED FOR MATCHING VARIABLES OR RISK FACTORS)

Organ System	Group	Number of Abnormalities 0	1	2	3	4	5-6	Unadjusted P Values
General Health	RH	791	228	18	-	-	-	0.27
	C	573	186	8	-	-	-	
Malignancy	RH	997	48	0	-	-	-	0.01
	C	755	17	1	-	-	-	
Reproductive	RH	374	198	-	-	-	-	0.34
	C	263	158	-	-	-	-	
Neurological		0	1	2	3	4-9		
(Full Data Subset)	RH	113	268	238	126	84		0.17
	C	112	179	186	92	57		
(Subset with 1 Missing Parameter)	RH	59	64	36	20	6		0.79
	C	40	46	27	9	6		
Psychological		0	1	2	3	4	5-6	
(Full Data Subset)	RH	341	301	121	10	-	-	0.29
	C	243	234	75	3	-	-	
(Subset with 1 Missing Parameter)	RH	143	114	11	-	-	-	0.38
	C	129	83	6	-	-	-	
Hepatic								
(Full Data Subset)	RH	184	206	143	68	26	3	0.45
	C	134	134	94	54	18	7	
(Subset with 3 Missing Parameters)	RH	114	134	90	44	29	4	0.27
	C	74	115	77	42	24	0	
Dermatologic	RH	470	575	-	-	-	-	0.97
	C	347	426	-	-	-	-	
Cardiovascular	RH	491	324	151	53	16	6	0.92
	C	365	232	117	42	12	2	
Hematologic	RH	428	432	147	35	3	-	0.59
	C	341	311	98	20	3	-	
Pulmonary	RH	655	289	52	32	12	-	0.05
	C	463	232	56	15	4	-	
Renal	RH	1002	42	1	-	-	-	0.70
	C	740	31	2	-	-	-	
Endocrine	RH	787	207	36	6	-	-	0.20
	C	551	182	33	4	-	-	

These data demonstrate statistically significant group differences only for malignancy (a result of the identified increase in skin cancer in the Ranch Hand Group) and in pulmonary function (due to more abnormalities in the comparison group). All other analyses were not statistically significant. The reader is cautioned that the data in Table XVII-9 are crude counts, unadjusted for the matching variables or risk factors known to affect organ system parameters. The number of abnormalities per organ system may be considered a crude index of severity. All individuals and their abnormality counts were summed, regardless of the degree of completeness of their data. The frequency distribution of these abnormalities is shown in Figure XVII-1.

Figure XVII-1

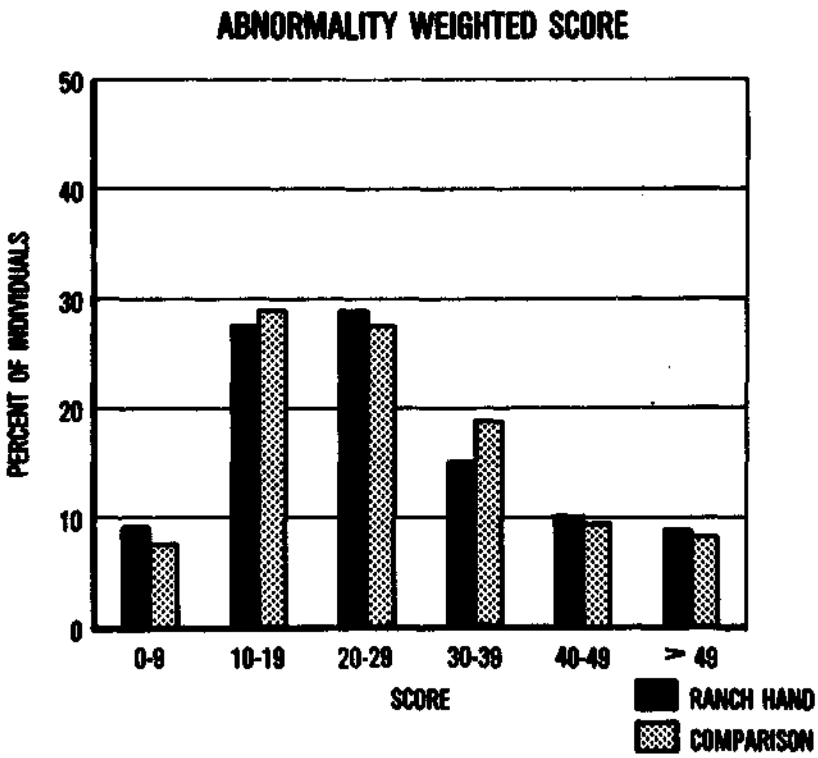


There was a maximum of 61 abnormalities in this analysis. The median number of abnormalities in both the Ranch Hand and comparison groups was seven. There were 0.96% of the Ranch Handers and 1.55% comparison individuals who had no abnormalities, and 2.58% and 2.07%, respectively, with 16 or more abnormalities. Log linear analysis of these distributions revealed no differences between the groups for numbers of abnormalities or degree of completeness of data (P values of 0.26 and 0.59, respectively).

b. Weighted Score of Individual Abnormalities

The count of abnormalities (Table XVII-9) was subjected to a weighting scale of 1 to 10 depending on the clinical seriousness of each abnormality. While such weighting is arbitrary, the resulting data serve as a complementary analytic technique to the basic count of abnormalities in which, for example, acne is considered to be equivalent to systemic cancer or a major ECG abnormality. The assignment of a weight to each abnormality was made before organ system results were known. Appendix VII contains a listing of all parameters and their relative weight scores for each organ system. The weighted score histogram is depicted in Figure XVII-2.

Figure XVII-2



Scores between zero and nine were achieved by 9.09% of the Ranch Handers and 7.24% of the comparisons, with 8.80% of the Ranch Handers and 8.02% of the comparisons scoring above 50 (out of a maximum possible score of 236). The median score was in the 20 to 24 range for both groups. The weighted score analysis showed statistical significance for cancer, again due to the aggregation of skin cancer in the Ranch Hand group. Statistical differences of interest were noted for renal disease (P = 0.09), general health (P = 0.114), and hepatic disease (P = 0.11). The relevance of these P values is minimal in view of the predominantly negative analyses observed in the clinical chapters. All weighted scores were combined across clinical areas and no statistically significant differences were noted (P = 0.20).

From these analyses on crude and weighted abnormalities, it is clear that there were not significantly more ill or more severely ill individuals in the Ranch Hand group than in the comparison group.

c. Physical Examination Diagnostic Codes

The diseases or conditions listed by the diagnostician in the diagnostic summary of the review of systems, the medical history, and the physical examination were coded according to the 9th ICD-CM manual. These diseases were coded as being reported by history, or suspected or actually diagnosed conditions. One individual could account for more than one diagnosed disease or condition. The diagnostician listed 219 suspected diseases among the 1045 Ranch Handers and 160 suspected conditions in the 773 original comparisons (P = 0.91). In both groups, there were 0.21 suspected diagnoses per individual. Similarly, 1949 definitive diagnoses were made in the Ranch Handers and 1437 in the original comparisons yielding an average of 1.87 diagnoses per Ranch Hander and 1.86 per comparison individual (P = 0.96). While the mean numbers of suspected and definitive diagnoses were essentially the same in both groups, the mean number of diseases and conditions reported by the participants were different in the two groups. There were 113 diseases reported by history in the Ranch Handers, but only 57 in the comparisons (mean number of conditions of 0.11 per person and 0.07 per person (P = 0.02), respectively). The similarity in diagnosed and suspected conditions in the two groups parallels the findings in the analysis of examination abnormalities. The difference in reported conditions may reflect differential reporting, or actual difference in past health. However, if past illness was different in the two groups, these experiences have apparently not resulted in long-term sequelae detected at the examination.

3. Summary

The anecdotal comments of the examining physicians and psychologists suggested that the study participants were remarkably healthy both physically and mentally for a group of mid-aged men. These comments were made about the entire group of participants based on the medical experience of each examiner, without knowledge of which individuals were Ranch Handers and which were comparisons. The statistical analyses discussed in this chapter support the clinical impressions of the examiners.

Both the Ranch Handers and the original comparisons had somewhat similar health habits, although significantly more Ranch Handers are current cigarette smokers and more had reported smoking marijuana in the past. The two groups were also similar in risk-taking activities, religion, education, income, and military status.

The distribution of identified health abnormalities by individual, and the weighted scores of these abnormalities were not significantly different in the Ranch Hand and comparison groups. Similarly, the mean number of diagnoses per individual at the conclusion of the examination was not different in the two groups.

Overall, the health of individuals in the two groups appears to be quite comparable. As individuals, they seem to be in quite good health for men of their age. These findings and observations are most likely a result of the healthy worker effect, previously noted in the baseline mortality study.

Chapter XVIII

FUTURE COMMITMENTS

The large volume and complexity of the data collected during this baseline phase of the Ranch Hand II study have made it difficult to completely fulfill all aspects of the analytic plan envisioned in the study protocol. While most of the major anticipated analyses have been completed and included in this report, other important tasks remain to be done. The results cited in this report logically lead toward a commitment by the USAF and the study principal investigators to pursue further evaluations of these data, and follow the study participants over time. There are 5 key areas requiring additional effort: (1) database refinement, (2) definition of requirements and examination refinements for the follow-up phase of the study, (3) refinement and expansion of exposure indices (4) additional statistical analyses and (5) collaborative activities with other organizations involved in herbicide/dioxin research.

1. Database Refinement

The database derived from the questionnaire and from the physical examination was very extensive in size and scope, and a quality control program was initiated to identify coding, keypunching, and editing errors in the database provided by the contractors. This data validation has been an on-going task, and is not yet complete in some areas. After the remaining questionnaire and physical examination data have been validated by comparison with the source documents, epidemiologic and statistical analyses of these data will be completed. Additionally, validation of illnesses and conditions reported on the in-home questionnaire will continue to be accomplished as medical records and birth certificates are received. Methods of validating smoking histories, and a reassessment of flying status and its impact on compliance will be pursued. The completion of this process will provide a verified database for subsequent analyses. This process will also allow an assessment of the degree of differential reporting present in the study.

2. Follow-up Examination Requirements

One of the purposes of the baseline phase was to identify clinical areas requiring in-depth evaluation in the follow-up portions of the study. Focused questionnaire and physical examination formats will be developed for use during the reexamination scheduled for 1985. At that time detailed evaluation of skin cancer, and known risk factors affecting its occurrence will be obtained. Additional data on fertility and reproductive history will be gathered and updates of conceptions and live births occurring since the baseline questionnaire will be obtained. The cardiovascular status of the participants will also be closely examined, using doppler measurements of peripheral pulses and electrocardiographic monitoring during stress testing. New, fully validated psychological scales will be used to assess additional psychological parameters such as sleep patterns. Further immunologic evaluations with strict laboratory quality control will also be accomplished. Steps will also be taken to insure that all participants comply with dietary and 24-hour urine collection requirements. At the time of the follow-up physical examination, all participants will be requested to authorize an autopsy at the time of their deaths and have copies of those reports and tissue specimens provided to the Air Force. The participants will also be asked to forward copies of hospitalization summaries and other significant medical events to the Air Force for inclusion in their records at Brooks AFB.

3. Exposure Index Refinement

The index of exposure to phenoxy herbicide and dioxin used in this report is not as complete or refined as planned in the study protocol. As it is currently calculated, each of the major occupational categories (Officers, Enlisted Flying, and Enlisted Ground) must be analyzed separately since the index is not necessarily equivalent in each category. A series of flights in a C-123 aircraft is planned. The aircraft will be configured and flown to simulate the Vietnam spray missions and a herbicide simulant will be released. Industrial hygiene sampling techniques will be used to measure differential exposure for aircrewmembers, ground support personnel, and administrative staff members. These data will then be used to calculate a weighting factor for use in the exposure index. In this way, a common index can be applied to all 3 occupational categories. The individual records of flying time ("Form 5's") will be used wherever possible to more clearly define the opportunity for in-flight exposures. Adjustment of the exposure analyses for confounding factors such as age and time spent in Southeast Asia will also be conducted to refine the index and make it more specifically a measure of herbicide exposure. This exposure index will also be modified to assess the degree of exposure to other chemicals such as arsenical herbicides (Herbicide Blue) and malathion.

4. Additional Statistical Analyses

Expanded statistical analyses and procedures are planned on the baseline data of this study. More detailed statistical power estimates will be developed for the analyses contained in this report, and an overall assessment of the ability of this study to detect adverse health effects in the populations studied will be made. Specifically, the analyses of reported and verified birth defects will be reaccomplished with the nature of the anomalies categorized as severe, moderate, and of minor medical consequence. The defects will also be classified as being congenital or teratogenic in origin. The results of the semen analyses and the father's occupation will also be considered. Efforts will be made to more fully define and correct sources of potential bias in the subsets of the comparison group so that all analyses can be conducted using the entire group of comparison individuals. This will maximize study power, and allow the use of the replacement strategy outlined in the protocol. Additional matched pair analyses will also be conducted in each clinical area, thus taking full advantage of the most powerful statistical techniques. The full spectrum of clinical end points and covariables will be analyzed as well. Case by case reviews of individuals with testicular, bladder, oropharyngeal, and skin cancer and those with pulse abnormalities will be conducted. This review may highlight additional risk factors and may suggest alternative epidemiologic and statistical methodologies for subsequent reanalysis (e.g., case-control studies).

Other techniques will be used to address correlations between clinical areas in the data. An organ system does not operate independently, and interactions between systems will be evaluated in subsequent reports. The effects of differential reporting are potentially significant in this study, and analyses aimed at differences in reporting between groups, and between study participants and their spouses will be evaluated. Questionnaire data was collected from the next-of-kin of deceased individuals and from totally noncompliant individuals, and time constraints have not permitted an analysis of these data. However, these are potentially valuable sources of information and appropriate evaluation will be conducted as time permits. Additional testing using more multi-variate techniques, expanded model-fitting, and goodness-of-fit testing will also be carried out via contract.

5. Collaborative Activities

Over the past 5 years, the principal investigators have worked closely with other organization and scientists involved in the herbicide/dioxin issue, and these collaborative activities will be strengthened and expanded. The common problems encountered by this study and the studies of Vietnam veterans being conducted by the Centers for Disease Control and the Veterans Administration can be more effectively resolved through the sharing of approaches and solutions. Collaboration has benefited all of these studies in the past, and should continue to be of benefit in the future. In addition to U.S. governmental agencies, the principal investigators have interacted with the epidemiologic staffs at DOW Chemical Company, Monsanto Company and with researchers in Australia, New Zealand and Europe. The value of these interactions cannot be overstated, and these contacts will be maintained as the study progresses. More importantly, a closer working relationship will be developed between the principal investigators and the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicide and Contaminants. Continued coordination with this panel will be invaluable as the complex findings of this study emerge over time.

Chapter XIX

INTERPRETATION OF STUDY RESULTS AND CONCLUSIONS

1. Introduction

This section presents a cautionary note to both scientific and lay readers who may wish to assert that this study, in whole or in part, is supportive or nonsupportive of a causal relationship between exposure to Herbicide Orange (and its dioxin contaminant) and adverse health. It is important to recognize that this observational study cannot prove the "negative," nor can it be construed as "definitive" science. The process of determining causality is complex and must entail a methodical consideration of many factors (Lilienfeld and Lilienfeld, 1980).

2. Causality Factors

In general, the following factors are very important in making an inference of causality: strength of association; dose-response; biologic plausibility; consistency; time relationships; specificity; and coherence. In an epidemiologic study, not all these factors are required to be present in order to make a correct inference, but clearly, substantial conflict between one or more factors casts doubt on an inference of causality.

In this study, numerous group differences (associations) were detected and expressed in terms of probability (P) values. In any given analysis, statistically significant P values (<0.05) represent the strength of the association, but in and of themselves, do not imply an herbicide causation. As expected under the null hypothesis, most a priori hypothesis tests were negative ($P > 0.05$), but the validity of these findings must be assessed by the power of the given test. As expected, many positive associations were found in the clarifying analyses, or as expressions of the influence of specific risk factors (e.g., age, smoking, etc.). Highly significant associations must also be viewed in the context of relative risk. A very significant association with a relative risk of less than two is generally of minor interest from the traditional epidemiologic perspective. In this study, only four objectively determined group differences of $P < 0.05$ had a relative risk of two or greater. Moreover, statistically significant differences in the group means of a laboratory parameter were often detected, but the overall distributions were similar, the values were within normal range, and the clinical relevance of these shifts was not readily apparent (e.g., LDH, testosterone, T_3, etc.).

A positive linear dose response relationship is a substantial feature in establishing a cause and effect association. A careful counting of the 388 exposure index analyses cited in this report shows that only 11% are statistically significant, and only 2.8% are increasing from low to high exposure. While these proportions are suggestive of chance associations, this possibility should be modified by the fact that positive exposure analyses, although not totally consistent throughout all occupational categories, tend to aggregate in only several of the organ systems. Additionally, it is recognized that the exposure index has not been fitted to the most specific format, as further experimental studies are still in progress. Thus, the exposure index used herein is a very indirect measure of exposure, making these analyses less certain than the observed group differences. Numerous other subcategorical exposure analyses (also predominantly negative) were accomplished, but were not included at the discretion of the author. Descriptive opinions of the positive exposure associations were often the sole choice of the responsible principal investigator within each chapter.

The time interval from herbicide exposure to onset of subclinical or clinical manifestations is an important concept for proper interpretation of these study findings. The observational period for the detection of possible latent health effects ranges from 10-20 years for all Ranch Handers. While 10-20 years may be insufficient time for the induction of many systemic cancers, and possibly skin cancer, clearly it is of sufficient length to have already "caused" transient biochemical aberrations, birth outcome abnormalities, fertility problems, chloracne, porphyria cutanea tarda, neurologic sequelae, psychological deficits, etc. Thus, if the above acute/subacute conditions are found attributable in these data, it must be acknowledged that the end result of many of the disease processes is being observed. That notion must be reconciled with essentially identical mortality rates in both groups to date, as many of the proposed diseases would most likely have exerted a subtle mortality influence. Alternatively, the suggestion that the release of dioxin from fat may result in slow systemic poisoning, if true, may account for a delay of clinical manifestations beyond classically accepted latent periods. Another influential time-onset relationship is that of "crossover," i.e., a sequential time-disease association based upon a linkage to a pulsed exposure. While many pre/post-SEA analyses have been performed in this study, reapplication of exposure to herbicides (to complete the crossover) via non-SEA vocations or avocations has not, as yet, been exploited.

Other causal factors merit comment. The finding of no cases of soft tissue sarcoma, porphyria cutanea tarda or chloracne in the Ranch Hand group may reflect a lack of specificity and/or a weak toxicity of the received dose of the putative agent (dioxin), or may reflect the low statistical power to detect group differences for these diseases in this study. The absence of these three diseases may also suggest that a synergism with a yet-to-be-discovered factor is required to induce disease. Findings of this study are, as yet, not fully consistent with other human dioxin studies performed in industrial populations. However, this inconsistency may be attributable to different exposure levels. In terms of biological plausibility, there is no discernible syndrome or symptom cluster that has emerged from this study that makes sense, has an identifiable pathogenesis, or has an analogous animal model. A systemic poisoning theory carries with it the expectation of finding more biochemical abnormalities than were detected in this study.

3. Other Factors

Chloracne has been proposed as a prerequisite to systemic disease. This premise is not wholly consistent with spectrum of illness concepts or other studies which have suggested attributable soft tissue sarcoma in predominantly nonchloracne populations. However, if the premise is true to the extent that the induction of chloracne represents moderate to high exposures to dioxin, then overall, it may be inferred that the Ranch Hand group (with no chloracne) has received relatively low exposure vis-a-vis industrial populations. Assuming a dose-response hierarchy, this inference may be extended to the contemplated studies of U.S. military ground personnel, for if the Ranch Hand study is deemed "negative," so probably will be the other studies of comparable size.

The question of the validity of this study is paramount. Overall, the processes of data collection have been quite good. To the extent possible, biases have been minimized in both the data collection and data analytic phases. Notwithstanding, a general predominance of adverse findings can be noted in the Ranch Hand group. A closer inspection of this aggregation suggests that most statistically significant findings are found in the subjective data sets, as contrasted to the objective measures. Many of these subjective findings in the Ranch Hand group are in various stages of medical record verification at this time. Unfortunately, some areas, e.g., psychological testing by questionnaire, can never be totally verified. Throughout this study, there is a suggestion of differential reporting (MMPI K and Hypochondriasis scales), albeit unanalyzed, that must temper the interpretation of the subjective results. For the objective data, there is good evidence that the laboratory measurements and the clinical assessments were reasonably accurate. This study has duplicated the classical effects of numerous risk factors (age, smoking, alcohol, etc.) on the clinical measurements throughout all organ systems. The detected effects of age and smoking in the functional and count immunologic tests are new observations, to the best of our knowledge. Thus, the effects of these risk factors have been taken into account throughout the study and lend strong credence to the accuracy of the overall group associations, whether statistically significant or not. It is our belief that this physical examination has reflected the true health status of all participants and groups to the maximum extent possible.

4. Conclusions

a. Preface

This section places into context the thousands of statistical tests which have been accomplished on the enormous data bases generated by the population ascertainment efforts, and the administration of the in-home questionnaire and the physical examination. The total baseline study, including all preparatory tasks and the Baseline Mortality Report, has spanned more than 5 years, has required approximately 100 man-years of in-house work, and has cost about $11M in direct and indirect costs. The Ranch Hand study has been characterized by solid resource support and stringent timetables throughout all levels of government, intense media interest, and outstanding participation of the study subjects. As part of the mosaic of all dioxin research, the Ranch Hand study has been directed to the herbicide-health effect issue in veterans, and specifically, to heavily exposed Air Force personnel.

b. Study Performance Aspects

Of all live Ranch Hand and comparison individuals who were selected for this study, almost all (99.5%) were contacted, eliminating a major element of bias concern. Participation in the in-home questionnaire was 97% and 93% for the Ranch Handers and comparisons, respectively; and similarly 87% and 76% for physical examination. Differential compliance to the examination may have introduced a participation bias, a bias that is potentially related to the true health status of the participant. Age, race, participation in flying, and military status were also significant factors in determining attendance at the examination, but the relative contribution of each factor has not as yet been determined. Traditionally, individuals in either military or civilian commercial flying occupations do not readily volunteer for physical examinations that might disclose even minor ailments that jeopardize their flying careers.

Early in the study, it was discovered that 18% of the comparison group was ineligible for the study because of inappropriate selection due to a computer programming error. Some selected USAF organizational units containing cargo-hauling aircraft were found not to be engaged in RVN duties (a study requirement). Thus, the direction of the error was for overselection and not for underselection of the comparison group. Ineligible individuals were removed from the randomly ordered comparison set. The replacements for the ineligibles were the next-in-line proper comparisons. For both these "shifted" comparisons and the next-in-line comparisons who were also used as substitutes for noncompliant individuals, later statistical analyses suggested that they differed from the original eligible comparisons in a variety of subtle and often opposite ways. Because of the possible bias suggested in their use, and because of the time constraints of this report, a conservative management decision was made to base the bulk of statistical tests upon a contrast of the original comparisons to the Ranch Hand group. Several analyses, using the entire comparison group, were also performed and found not to differ consistently from the analyses based upon the original comparison group. For those analyses which showed differences between the original versus the total comparison group contrast, it is unclear whether these differences are primarily due to true subset variances or to a sample size effect. A full clarification of the complex biases (selection, compliance, overreporting, etc.) must be conducted before the first follow-up phase of the study.

Most of the stringent quality control aspects of the study were monitored and maintained throughout the data collection phases. As a USAF contract requirement, all contractors were required to maintain "blindness" with respect to the exposure status of each individual, thereby reducing examiner bias to an absolute minimum. In addition, by contract all data are the property of the USAF. Study codes were not provided to the contractors.

c. <u>Clinical Aspects</u>

In terms of overall health, the Ranch Handers perceive their state of health to be poorer than that of the comparisons. This finding parallels the examiner's independent assessment. Percent body fat is similar in both groups as are the hematocrit determinations. A higher proportion of abnormal red cell sedimentation rates is found in comparisons under 40 years of age. The proportions are the same in both groups older than 40. The sedimentation rate, hematocrit, percent body fat, self-perception of health, and age are associated pairwise irrespective of group; these relationships are expected as all variables are traditional indicators of nonspecific illness.

There are no significant group differences for malignant or benign systemic tumors. One case of soft tissue sarcoma is noted in a member of the comparison group. A slight nonsignificant aggregation of genitourinary cancers is identified in the Ranch Hand group, and an aggregation of digestive system cancers is observed in the comparison group. Two Ranch Hand bladder cancers are noted at earlier-than-expected ages. A borderline association between systemic cancer and smoking is observed in both groups. Significantly more nonmelanotic skin cancer is observed and verified by medical record review in the Ranch Handers. The predominant cancer, basal cell carcinoma, is the most common skin cancer in the U.S. White male population, and a proper excision is curative. While this finding is of interest, it is emphasized that these data are not adjusted for sunlight exposure, the recognized primary cause of these cancers. This analysis must await more complete data to be collected at the first follow-up examination. Overall there is no consistent data to show that the Ranch Handers are developing uncommon systemic cancers, or cancer in unusual sites, or at a younger age. Both systemic and skin cancers in the Ranch Hand group do not correlate consistently with the herbicide exposure index.

The fertility and reproductive analyses show mixed findings. As these results are largely based upon subjective self-reports, and must be verified by complete medical record and birth certificate reviews, the findings are judged preliminary at this time. A semen analysis on those participants willing and able to provide a specimen shows essentially identical sperm counts and percent abnormal forms between groups. The finding of an increase in sperm count by age is discounted as physiologically significant because of concomitant noncompliance by increasing age. Four measures of fertility show no difference between the Ranch Hand and comparison groups: number of childless marriages; couples with the desired number of children; the fertility index; and the infertility index. There are no significant findings in conception outcomes for miscarriages; stillbirths, induced abortions, or live births. With respect to live birth outcomes, no group differences are observed for prematurity, learning disability, or infant deaths. Birth defects, as cited by parental history, show no group differences for severe or moderate classifications; however, for minor birth defects (simple birth marks, birth rashes, port wine stains, etc.) Ranch Hand offspring show a significant excess. Reported neonatal deaths and physical handicaps significantly predominate in the Ranch Hand group when contrasted to the full comparison group. All analyses are adjusted for as many of the relevant risk factors as possible, e.g., maternal age, maternal smoking, maternal use of alcohol, paternal age, pre/post-RVN service, etc. Herbicide exposure analyses show several findings of statistical significance but the patterns of association are not fully consistent across all occupational categories.

A thorough neurological assessment of the cranial nerves, peripheral nerves, and central nervous system functioning does not disclose any substantive Ranch Hand-comparison group differences. Past history of neurological disorders is similar for both groups. An increased proportion of abnormal Babinski reflexes are noted in the Ranch Handers but this finding is not statistically significant. Detailed nerve conduction velocities are not associated with group membership but are profoundly influenced by alcohol and diabetes. Similarly, abnormalities in sensation to light touch, vibration, and two reflexes are related to abnormal postprandial glucose levels. Exposure index analyses are predominantly negative.

Detailed psychologic evaluations from the in-home questionnaire and physical examination show consistent findings. Educational level of the participant profoundly influences most all of the subjective test results. Due to the inherently high correlation between military rank and educational level, these variables are considered interchangeable. It is emphasized that the majority of psychologic data are based upon highly subjective self-reporting, most of which can never be fully verified by medical record reviews. There are no group differences for reported past emotional or psychological illnesses. However, the high school educated (mostly enlisted) Ranch Handers demonstrate significant findings or deficits in the following categories: fatigue, anger, anxiety, erosion, fear, startle, psychosomatic behavior, hypochondria, masculinity, and mania/hypomania. It is noted that the high school educated comparisons exhibit a higher degree of denial in most of these categories. These findings are not observed in the college educated Ranch Handers (mostly officers). The Ranch Hand group demonstrates significant hypochondria, depression, hysteria and schizophrenia vis-a-vis the comparison group, after adjustment for education. In sharp contrast, there are no substantial group differences for the more objective functional and performance psychologic tests (e.g., Halstead-Reitan battery, IQ testing). Almost all exposure index analyses are negative. In full context, differential reporting is strongly suggested, albeit unproven. The roles of an overreporting bias and the Post-Vietnam Stress Syndrome will be clarified in subsequent follow-up psychological evaluations.

The hepatic status is assessed by 9 biochemical tests and a variety of questionnaire and medical record data. The results are mixed. Ranch Hand GGPT and LDH levels are slightly higher while cholesterol levels are lower than the comparisons. Alcohol history is associated with most enzymatic elevations in both groups. Ranch Handers report significantly more skin changes compatible with a historical diagnosis of porphyria cutanea tarda (PCT). However, laboratory determinations for delta-aminolevulinic acid, uroporphyrin and coproporphyrin are similar between groups and no cases of PCT were diagnosed at the physcial examination. Reported miscellaneous liver disorders, verified by medical record reviews, are found significantly more in the Ranch Handers. The exposure index analyses are generally inconsistent.

A comprehensive dermatologic evaluation reveals no substantial findings in the Ranch Hand group. No cases of chloracne are diagnosed clinically or by biopsy of suspicious lesions. Questionnaire data show that the incidence, severity, duration, and anatomic locations of past acne do not portray a pattern consistent with significant historical chloracne in the Ranch Handers. The classical "eyeglass" distribution of acne (suggesting chloracne) is the same in both groups. Historical acne correlates with the total cumulative acne found at physical examination. All exposure index analyses are negative.

Examination of the central cardiovascular system reveals no remarkable differences between the groups for systolic blood pressure, diastolic blood pressure, abnormal electrocardiograms, past versus present electrocardiograms, or abnormal heart sounds. As expected, abnormalities in most of these parameters are significantly associated with age, smoking, and a past history of heart disease. The three risk factors: age, smoking, and cholesterol level are strongly associated with each other, and HDL cholesterol is significantly influenced by percent body fat and smoking. An analysis of questionnaire data shows that the Ranch Handers are not having premature heart attacks or generalized heart disease, although subset analyses show differing age and smoking effects. As an unexpected finding, two peripheral pulses are significantly diminished or absent in the Ranch Handers, and several other pulses show weak group differences. Clarifying statistical analyses show that the the aggregate of Ranch Hand peripheral pulses, predominantly leg pulses, are significantly associated with age, past smoking, current smoking, and verified past heart disease. The weak but similar directional findings in the Ranch Hand carotid and femoral pulses are assigned more significance in view of the peripheral pulse observations. State-of-the-art measurement techniques and a specific medical questionnaire will be used to determine the relevance of these pulse deficits at the first follow-up examination. Detailed herbicide exposure analyses show no associations to any of the central or peripheral cardiovascular findings.

Detailed immunological tests, via B and T lymphocyte enumeration and lymphocyte function studies on a randomized subset of all participants, do not demonstrate significant group differences. Because of the high variability of the quality control data, an independent peer review panel evaluated testing methodology and established criteria for analysis. The numbers of T_{11}, T_3, T_4, T_8, B_1, positive cells and total lymphocyte counts are similar in both groups. Smoking history is observed to significantly affect the T_{11}, T_3, T_4, T_8, marker counts and the total lymphocyte count. Age is seen to affect the T_8 count and the total lymphocyte count. No group differences are observed for the functional studies using phytohemagglutinin, concanavallin A, pokeweed mitogen, and tetanus toxoid. Although the baseline proliferation rate (Control #1) was significantly lower in the Ranch Handers, the biologic relevance of this finding is unclear, particularly in the absence of group differences for concanavallin A and phytohemagglutinin stimulation studies. Age is observed to profoundly affect concanavallin A and phytohemagglutinin results while smoking history is seen to significantly influence pokeweed mitogen results. Because of the overall variability of quality control data, interpretation of a specific individual's immunocompetence is not attempted.

Of 8 measured blood elements and parameters, the mean corpuscular volume and the mean corpuscular hemoglobin level are statistically significantly elevated in the Ranch Hand group, but the relative differences are exceptionally minor and are not of clinical relevance or understanding at this time. Seven of the 8 blood measurements are significantly affected by smoking history. Several exposure index analyses demonstrate positive correlations but a consistent pattern by occupational strata is not observed.

There is no group difference in the distribution of reported past pulmonary disease. Forced expiratory volume for one second and forced vital capacity measurements obtained at the physical examination do not reveal group differences that are consistent in character. There are age/smoking/exposure interactions but it is not possible to further delineate these findings at this time. Several statistically significant herbicide exposure index analyses do not conform to classic dose-response relationships.

Ranch Handers report significantly more kidney disease than the comparisons but this history is not corroborated by 6 laboratory measurements obtained at the physical exam. Proteinuria is of borderline significance in the comparison group. Creatinine clearance may be considered of borderline significance in the Ranch Handers, depending on the laboratory value chosen to determine the abnormal category. Because of the substantial problem of compliance to the 24 hour urine collection, little credence is assigned to the creatinine clearance results. Age is observed to influence the blood urea nitrogen and urine specific gravity results while diabetes affected only the specific gravity results. Herbicide exposure analyses are essentially unrevealing.

A comprehensive assessment of thyroid function and insulin and testosterone production show mixed results. Distributional shifts are noted in thyroid function between the Ranch Hand and comparison groups but the test results are generally within the limits of normal values. There are no group differences for diabetes as determined by abnormal 2 hour postprandial glucose levels. Age and percent body fat determinations are associated with abnormalities in T_3 uptake, 2 hour postprandial glucose levels, and testosterone levels. Herbicide exposure analyses show a variety of positive correlations but many are inconsistent across occupational strata.

Evaluations of personal habits and individual health show that Ranch Handers currently smoke cigarettes more than the comparisons, equally participate in high risk sports activities, and have a similar background of traumatic injuries. An unrefined assessment of the total number of abnormalities found at the physical examination show no Ranch Hand aggregations in the high range nor do arbitrary clinically weighted scores. Overall, both groups are comparable in most health respects, and are probably faring better than similarly aged men in the general population.

d. Final Conclusion

This study has disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and to their families at this time, because this study has not identified statistical group differences for illnesses commonly attributed to dioxin exposure. The data herein suggest that group differences exist which tend to favor the comparisons, but the cause and clinical relevance of these differences is unclear. This baseline 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.

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Appendix I

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Appendix II

ADVISORY COMMITTEE ON SPECIAL STUDIES RELATING TO THE POSSIBLE LONG-TERM HEALTH EFFECTS OF PHENOXY HERBICIDES AND CONTAMINANTS

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Appendix III

CONTRACT MANAGEMENT

The Aerospace Medical Division, Air Force Systems Command, Brooks AFB TX, was designated as the primary management agency responsible for the Air Force Health Study. The program is managed by the Commander, USAF School of Aerospace Medicine, with scientific, technical, and business management support from the Epidemiology Division and the Data Sciences Division of the USAF School of Aerospace Medicine and business support from the Director for Systems Acquisition, Aerospace Medical Division, respectively. The Commander, USAF School of Aerospace Medicine, coordinates business and technical inputs from the interfacing organizations and consolidates program status and direction. He is responsible for informing higher headquarters of management or technical situations which could impact the success of the program.

The 3303rd Contracting Squadron, Air Training Command, Randolph AFB TX, provides all procurement support to the Ranch Hand II Program. Contracted efforts, to date, have included software development, statement of work preparation, questionnaire development, questionnaire administration and the conduct of physical examination. To the maximum extent practical, fixed price contracts with cost reimbursement for travel, lodging and stipend expenses were used. The contractor(s) provided data as required to the contracting agency and the Program Manager. Reports were provided on technical progress, expenditure of funds, and overall program progress against the contractual schedules. Data were used to assess program progress and to initiate corrective actions where required.

A contract to assist in the development of a statement of work for the questionnaires was let to Research Statistics, Inc., Houston TX, at a cost of $11,900.

The study questionnaire was developed by the National Opinion Research Center, New York NY, a nationally recognized survey research firm. A sole source contract was awarded on 26 September 1980 and was concluded on 31 July 1981 at a total cost of $348,000.

Louis Harris and Associates, Inc., New York NY, was competitively selected to administer the questionnaire and awarded a contract on 18 September 1981. The original effort was scheduled for completion in April 1982, but due to data collection as well as questionnaire/physical examination contractor interface requirements, the contract was extended to November 1982. The final cost for the questionnaire administration effort was $1.076 million.

A formal source selection process was also used to select the Kelsey-Seybold Clinic, P.A., Houston TX, as the single site for conducting the physical examinations. The initial contract period was scheduled for 10 months (23 November 1981 - 30 September 1982) but was extended to 15 December 1982. The total contract cost was $6.161 million, which included the physical examinations, travel expenses, lodging, meals and stipend allowances.

An Air Force on-site physician monitor in-briefed all study participants and conducted quality control checks on all medical aspects of the physical examination. Additional medical and contracting specialists periodically visited the examination site to ensure adherence to all aspects of the contract. All three contracting efforts were characterized by this type of close interaction and control.

Appendix IV

KELSEY-SEYBOLD NORMAL VALUE REPORT
BLOOD CHEMISTRY

AGE-ADJUSTED NORMALS

AGES	PARAMETERS
10 - 29 Years	BUN (mg/dl): 10-26
	Creat (mg/dl): 0.7-1.4
	Gluc (mg/dl): 70-115
	Chol (mg/dl): 106-210
	Trig (mg/dl): 30-140
	HDL (mg/dl): 32-72
	T Bil (mg/dl): 0.2-1.2
	D Bil (mg/dl): 0-0.36
	Alk Phos (U/dl): 2.5-9.7
	SGOT (U/L): 0-41
	SGPT (U/L): 0-45
	GGTP (U/L): 15-85
	LDH (U/L): 0-200
	CPK (U/L): 35-232
	Alcohol (mg/dl): None
30 - 39 Years	BUN (mg/dl): 10-26
	Creat (mg/dl): 0.7-1.4
	Gluc (mg/dl): 70-115
	Chol (mg/dl): 119-240
	Trig (mg/dl): 30-150
	HDL (mg/dl): 32-72
	T Bil (mg/dl): 0.2-1.2
	D Bil (mg/dl): 0-0.36
	Alk Phos (U/dl): 2.5-9.7
	SGOT (U/L): 0-41
	SGPT (U/L): 0-45
	GGTP (U/L): 15-85
	LDH (U/L): 0-200
	CPK (U/L): 35-232
	Alcohol (mg/dl): None
40 - 49 Years	BUN (mg/dl): 10-26
	Creat (mg/dl): 0.7-1.4
	Gluc (mg/dl): 70-115
	Chol (mg/dl): 131-265
	Trig (mg/dl): 30-160
	HDL (mg/dl): 32-72
	T Bil (mg/dl): 0.2-1.2

	D Bil (mg/dl): 0-0.36 Alk Phos (U/dl): 2.5-9.7 SGOT (U/L): 0-41 SGPT (U/L): 0-45 GGTP (U/L): 15-85 LDH (U/L): 0-200 CPK (U/L): 35-232 Alcohol (mg/dl): None
50 - years and older	BUN (mg/dl): 10-26 Creat (mg/dl): 0.7-1.4 Gluc (mg/dl): 80-125 Chol (mg/dl): 144-265 Trig (mg/dl): 30-190 HDL (mg/dl): 32-72 T Bil (mg/dl): 0.2-1.2 D Bil (mg/dl): 0-0.36 Alk Phos (U/dl): 2.5-9.7 SGOT (U/L): 0-41 SGPT (U/L): 0-45 GGTP (U/L): 15-85 LDH (U/L): 0-200 CPK (U/L): 35-232 Alcohol (mg/dl): None
Unknown	BUN (mg/dl): 10-26 Creat (mg/dl): 0.7-1.4 Gluc (mg/dl): 70-125 Chol (mg/dl): 106-265 Trig (mg/dl): 30-190 HDL (mg/dl): 32-72 T Bil (mg/dl): 0.2-1.2 D Bil (mg/dl): 0-0.36 Alk Phos (U/dl): 2.5-9.7 SGOT (U/L): 0-41 SGPT (U/L): 0-45 GGTP (U/L): 15-85 LDH (U/L): 0-200 CPK (U/L): 35-232 Alcohol (mg/dl): None

Appendix V

DEFINITION OF BIRTH DEFECTS, LEARNING DISABILITIES AND PHYSICAL, MENTAL OR MOTOR IMPAIRMENTS

Birth Defects

ICD-9 Code	Condition
740	Anencephalus and similar anomalies
741	Spina Bifida
742	Other nervous system anomalies
743	Anomalies of eye
744	Anomalies of ear, face, and neck
745	Bulbus cordis/cardiac septal closure anomalies
746	Other anomalies heart (valves)
747	Other anomalies of circulatory system
748	Other anomalies of respiratory system
749	Cleft palate and cleft lip
750	Other anomalies of upper alimentary tract
751	Other anomalies of digestive system
752	Anomalies of genital organs
753	Anomalies of urinary system
754	Certain congenital musculoskeletal deformities
755	Other anomalies of limbs
756	Other musculoskeletal anomalies
757	Anomalies of the integument
758	Chromosomal anomalies
759	Other and unspecified anomalies
216	Benign neoplasm of skin
228	Hemangioma and Lymphangioma, any site
239.2	Neoplasms of unspecified nature of bone, skin, connective tissue
363.2	Chorioretinitis
426.7	Wolff-Parkinson-White syndrome
524.0	Major anomalies of jaw size
550	Inguinal hernia gangrene
550.1	Inguinal hernia with obstruction, no mention of gangrene
550.9	Inguinal hernia, no mention of obstruction or gangrene
553.1	Umbilical hernia
553.29	Epigastric hernia
658.8	Amniotic bands (constricting bands)
685.1	Pilonidal Sinus or dimple
778.6	Hydrocele

Learning Disabilities (Developmental Delays)

313	Disturbance of emotions specific to childhood and adolescence
314	Hyperkinetic syndrome of childhood
315	Specific delays in development
317	Mild mental retardation
318	Other specified mental retardation
319	Unspecified mental retardation

Physical, Mental, Motor Impairments

760	Fetus or newborn affected by maternal conditions which may be unrelated to present pregnancy
761	Fetus or newborn affected by maternal complications of pregnancy
762	Fetus or newborn affected by complications of placenta, cord and membrane
763	Fetus or newborn affected by other complications of labor and delivery
764	Slow fetal growth and fetal malnutrition
765	Disorders relating to short gestation and unspecified low birthweight
766	Disorders relating to long gestation and high birthweight
767	Birth trauma
768	Intrauterine hypoxia and birth asphyxia
769	Respiratory distress syndrome
770	Other respiratory conditions of fetus and newborn
771	Infections specific to the perinatal period
772	Fetal and neonatal hemorrhage
773	Hemolytic disease of fetus or newborn, due to isoimmunization
774	Other perinatal jaundice
775	Endocrine and metabolic disturbances specific to the fetus and newborn
776	Hematological disorders of fetus and newborn
777	Perinatal disorders of digestive system
778	Conditions involving the integument and temperature regulation of fetus and newborn
270	Disorders of amino-acid transport and metabolism
271	Disorders of carbohydrate transport and metabolism
272	Disorders of lipoid metabolism
273	Disorders of plasma protein metabolism
274	Gout
275	Disorders of mineral metabolism
276	Disorders of fluid, electrolyte, and acid-base balance

277	Other and unspecified disorders of metabolism
278	Obesity and other hyperalimentation
279	Disorders involving the immune mechanism
340	Multiple sclerosis
341	Other demyelinating diseases of central nervous system
343	Infantile cerebral palsy
344	Other paralytic syndromes
345	Epilepsy
359	Muscular dystrophies and other myopathies
250	Diabetes mellitus

Appendix VI

PHYSICAL EXAMINATION FORMS

- Patient History and Health Questionnaire
- Conduct of the Examination (Internal Medicine)
- Neurological Examination
- Specialty Examination-Dermatology
- Pulmonary Function
- Diagnostic Summary

KS#__________________

NAME____ DATE: ________________________

PATIENT'S HISTORY AND HEALTH QUESTIONNAIRE

FAMILY HISTORY: HAVE ANY MEMBERS OF YOUR FAMILY EVER HAD THE FOLLOWING? IF SO, PLEASE CHECK BELOW AND NOTE WHICH FAMILY MEMBER.

	Mother	Father	Sister	Brother	Child
Diabetes					
Epilepsy					
Cancer					
High Blood Pressure					
Heart Disease					
Stroke					
Allergy					
Stomach Trouble					
Nervous Trouble					
Blood Disease					
Deformities					
Arthritis					
Other familial diseases:					

Please list: ____

FATHER: Living-Age ______ Condition of Health? ______________________
Dead-Age ______ Cause of Death? ______________________

MOTHER: Living-Age ______ Condition of Health? ______________________
Dead-Age ______ Cause of Death? ______________________

NUMBER BROTHERS: Living _____ Ages: ______________ Dead __________ Causes:

NUMBER SISTERS: Living _____ Ages: ______________ Dead __________ Causes:

ARE YOU MARRIED? ________ NO. OF YEARS ________ WIFE'S AGE: ______ HUSBAND'S AGE_____

Health of Husband or Wife?______________________________

If spouse dead, give age, year, and cause of death:______________________

Previous Marriages?__________ Gives dates:______________________

NUMBER OF CHILDREN: Boys: ______ Ages:______________ Girls: ______ Ages: ________

All Healthy?__________ Any dead?__________ Any birth defects?__________
If yes, explain______________________________

****

PLEASE LIST HERE ANY PHYSICAL OR NERVOUS COMPLAINTS WHICH YOU HAVE:________________

****

PERSONAL HISTORY

Allergy or severe reaction to medicines, foods, plants, chemicals, etc.: Please list:

____

____

____

List Average

Hours worked per day: __________

Hours sleep per night: __________

Days worked per week: __________

Days vacation per year: __________

Number cigarettes per day: __________

Other tobacco per day: __________

Cups coffee per day: __________

Alcoholic drinks per day: __________

Do you take regular exercise? __________

What is your usual weight? __________

What is the most you ever weighed? ______

At what age or year? __________

Have you lost or gained weight? ______

If so, how much? __________

PUT A CIRCLE AROUND ANY OF THE FOLLOWING CONDITIONS WHICH YOU NOW HAVE OR HAVE HAD IN THE PAST:

Skin Trouble
- Acne
- Excess hair growth
- Change of skin color
- Other __________

____

____

Cataracts
Tonsillitis
Sinusitis
Goiter
Hay fever
Asthma
Bronchitis
Pleurisy
Pneumonia
Tuberculosis
Breast Trouble
Heart Trouble
Stomach Trouble
Gallstones
Ulcer

Jaundice
Liver trouble
Hepatitis
Worms
Dysentery
Colitis
Hemorrhoids
Kidney Trouble
Kidney Stones
Bladder Trouble
Prostate Trouble
Syphyilis
Gonorrhea
Hernia (rupture)
Fainting
Fits or convulsions
Nervous Breakdown
Depression
Paralysis
Muscle Pain
Muscle weakness
Numbness

Loss of sensation
Loss of sex drive
Polio
Mumps
Measles
Rheumatic fever
Malaria
Arthritis
Gout
Anemia
Diabetes
Cancer or Tumor
Varicose Veins
Phlebitis
Rheumatoid Arthritis
Severe Arthritis
Systemic Lupus Erythematosus
Scleroderma

PAST HISTORY: Please list previous operations, injuries, serious illnesses, etc. and year; including those checked off above.

1. ______________________________
2. ______________________________
3. ______________________________
4. ______________________________
5. ______________________________
6. ______________________________

When was your last physical examination? __________ Any abnormality found? ____

Are you under any medical treatment now? __________ List any medications you take now or occasionally: ______________________________

____

PERSONAL PHYSICIAN:

Name ______________________________

Street Address ______________________________

City, State & Zip Code ______________________________

IF YOU HAVE HAD REPEATED CASES OF ANY OF THE FOLLOWING IN THE PAST YEAR, PLEASE CIRCLE

Pneumonia

Kidney Infections

Skin Boils

Other Infections (specify)

____

____

____

IF YOU HAVE ANY OF THE FOLLOWING COMPLAINTS, PLEASE CIRCLE YES, IF NOT, CIRCLE NO. THE DOCTOR WILL ASK ABOUT DETAILS LATER. ANSWER ALL QUESTIONS. IF IN DOUBT, GUESS YES OR NO.

Severe headaches or head pains	Yes	No
Do you have:		
Any disturbance in vision	Yes	No
Pain or discomfort in eyes	Yes	No
Wear glasses	Yes	No
Constant noise in ears	Yes	No
Hard of hearing	Yes	No
Ear ache with colds ( ) plane flights ( )	Yes	No
Chronic running ear	Yes	No
Chronic stuffy or runny nose	Yes	No
Need to use nose drops frequently	Yes	No
Bad nose bleeds at times	Yes	No
Frequent severe colds or sore throat	Yes	No
Any known dental problems	Yes	No
Soreness or bleeding of gums	Yes	No
More than a year since teeth checked	Yes	No
Sore mouth or tongue	Yes	No
Goiter or thryoid trouble	Yes	No
Thyroid test -- too high ( ) too low ( )	Yes	No
Feeling of lump in the throat	Yes	No
Need to take thyroid medicine	Yes	No
Hoarseness at times	Yes	No
Recent or chronic cough	Yes	No
Chronic coughing up of sputum	Yes	No
Ever coughed up blood	Yes	No
Ache all over	Yes	No
Having chills or fever	Yes	No
Severe soaking night sweats	Yes	No
Lived with anyone having T.B.	Yes	No
Worried about your heart	Yes	No
Blood pressure -- too high ( ) too low ( )	Yes	No
Pains in heart or chest	Yes	No
Pounding or skipping of heart	Yes	No
Heart starts racing suddenly	Yes	No
Shortness of breath or wheezing	Yes	No

Trouble getting a deep breath	Yes	No
Swelling ankles	Yes	No
Leg cramps in bed or sitting still	Yes	No
Leg cramps while walking	Yes	No
Pain or trouble with swallowing	Yes	No
Poor appetite -- recently ( ) always ( )	Yes	No
Nausea or vomiting	Yes	No
Vomiting of blood	Yes	No
Belching, bloating or indigestion	Yes	No
Yellow skin or eyes (jaundice)	Yes	No
Burning or hunger pains in stomach	Yes	No
Use antacids for stomach burning	Yes	No
Soreness or pain in stomach, abdomen	Yes	No
Suspect ulcers or stomach trouble	Yes	No
Cramps in stomach or low down	Yes	No
Loose bowels or diarrhea	Yes	No
Black or tarry stools (bowel movement)	Yes	No
Fresh or bright blood with stools	Yes	No
Mucus (slime or plegm) in stools	Yes	No
Constipation	Yes	No
Use laxatives ( ) or enemas ( ) frequently	Yes	No
Recent change in bowel habits	Yes	No
Rectal trouble or pain	Yes	No

List any foods which always disagree: ______________________________

____

Pain in the kidney region	Yes	No
Get up nights to urinate (Number of times _____)	Yes	No
Blood or pus in urine	Yes	No
Albumin in urine	Yes	No
Sugar in urine	Yes	No
Spells of frequent urination	Yes	No
Severe burning or pain on urination	Yes	No
Pains over bladder or low down	Yes	No
Trouble starting urine	Yes	No
Urinary stream has become weak	Yes	No
Hard to empty bladder completely	Yes	No
Lose control of passing urine	Yes	No
Painful or sore genitals (privates)	Yes	No

Swollen or painful joints	Yes	No
Stiffness of muscles or joints	Yes	No
Severe pains in arms or legs	Yes	No
Painful feet	Yes	No
Backache	Yes	No
Pains in neck	Yes	No
Easy to sunburn	Yes	No
Itch or rash (where?)________________________	Yes	No
Subject to acne	Yes	No
Subject to boils or infections	Yes	No
Subject ot athlete's foot, skin fungus	Yes	No
Subject to hives or skin reactions	Yes	No
Easy bleeding or bruising	Yes	No
Mole or sore which is not healing	Yes	No
Swelling, lump, or soreness anywhere on body (where?)_____ ____	Yes	No
Severe dizziness	Yes	No
Numbness or tingling (where?) ____________________	Yes	No
Twitching muscles (where?) ______________________	Yes	No
Generalized weakness	Yes	No
Muscle weakness	Yes	No
Nail biting	Yes	No
Sleep walking	Yes	No
Bed wetting after age 12	Yes	No
Chronically tired or overworked	Yes	No
Irregular living habits	Yes	No
Can't go to sleep or stay asleep	Yes	No
Nearly always in poor health	Yes	No
From sickly or nervous family	Yes	No
Considered to be a nervous person	Yes	No
Tremble and sweat easily	Yes	No
Have trouble making up your mind	Yes	No
Easily mixed up or confused	Yes	No
Clumsy or have frequent accidents	Yes	No
Feel sad, lonely or depressed	Yes	No
Cry often	Yes	No
Wish you were dead	Yes	No
Worry continually	Yes	No

Upset by little things	Yes	No
A perfectionist	Yes	No
Sensitive or feelings easily hurt	Yes	No
Often misunderstood	Yes	No
Often act on sudden impulse	Yes	No
Easily angered or have violent rages	Yes	No
Frequently keyed up and jittery	Yes	No
Easily scared by sudden noise	Yes	No
Have bad dreams or thoughts	Yes	No
Suspect a serious disease or cancer	Yes	No
Having trouble getting along with someone at home or work	Yes	No

Have you ever been exposed to any of the following substances or types of radiation? Exposure is defined as skin or respiratory contact more than one day's duration.

1.	Coal tar	Yes	No
2.	creosote	Yes	No
3.	anthrocene	Yes	No
4.	benezene	Yes	No
5.	benzidine	Yes	No
6.	naphthylamine	Yes	No
7.	aminodiphenyl	Yes	No
8.	mustard gas	Yes	No
9.	vinyl chloride	Yes	No
10.	chloromethyl ether	Yes	No
11.	arsenic	Yes	No
12.	chromates	Yes	No
13.	asbestos	Yes	No
14.	cutting oils	Yes	No
15.	trichloroethylene	Yes	No

16. Ultra-violet light (other than sun) . . . . Yes No
17. x-rays (other than routine) . . . . Yes No
18. ionizing radiation* . . . . Yes No

COMMENTS: For each "YES" exposure in the preceding list, please fill out the following:

1. Type of Exposure (coal tar, etc). ______________________
   A. Was exposure received on the job? Yes ______ No ______
   B. If yes, job title ______________________________
   C. If no, how exposure received ______________________________
   ____
   D. Circle frequency of exposure that best fits your experience:
      Daily Weekly Monthly Yearly
   E. In what year(s) were you exposed? ______________________________
2. Type of Exposure (coal tar, etc) ______________________
   A. Was exposure received on the job? Yes ______ No ______
   B. If yes, job title ______________________________
   C. If no, how exposure received ______________________________
   ____
   D. Circle frequency of exposure that best fits your experience:
      Daily Weekly Monthly Yearly
   E. In what year(s) were you exposed? ______________________________
3. Type of Exposure (coal tar, etc) ______________________
   A. Was exposure received on the job? Yes ______ No ______
   B. If yes, job title ______________________________
   C. If no, how exposure received ______________________________
   ____
   D. Circle frequency of exposure that best fits your experience:
      Daily Weekly Monthly Yearly
   E. In what year(s) were you exposed? ______________________________

CONDUCT OF THE EXAMINATION

NAME ______________________ DATE ______________________

DATE OF BIRTH (DOB) ______________________ CASE NO. ______________________

PHYSICAL EXAMINATION

---

1. General Appearance
   - a. Appearance/Stated Age: ( ) Younger Than ( ) Older Than ( ) Same As
   - b. Well-nourished ( ) ( ) Obese ( ) Under-nourished
   - c. Appearance of illness or distress ( ) Yes ( ) No
   - d. Hair distribution: ( ) Normal ( ) Abnormal
     Specify: ______________________

2. Height (cm)	Weight (Undressed) kg	Sitting Blood Pressure Right Arm at Heart Level
	Temp. Oral F.	Systolic ________ Diastolic ________

3. Pulse rate ________ Regular: ( ) Yes ( ) No
   a. Irregular ( ) b. Irregularly irregular ( ) c. VPBs per minute ________
   Describe any irregularities: ______________________

---

4. Eye Grounds: ( ) Normal ( ) Abnormal — Describe any vascular lesions, hemorrhages, exudates, or papilledema:
   - ( ) A-V nicking ( ) Hemorrhages
   - ( ) ↑ light reflex ( ) Exudates
   - ( ) Arteriolar spasm ( ) Disk Pallor
   - ( ) Papilledema ( ) ↑ Cupping

---

5. Arcus Senilis: ( ) Present ( ) Absent 5a. Abnormal Ocular Pigmentation ( ) Yes ( ) No

---

6. ENT: ( ) Normal ( ) Abnormal — Describe any abnormality:
   - Right Tympanic Membranes intact ( ) Yes ( ) No
   - Left Tympanic Membranes intact ( ) Yes ( ) No
   - Nasal Ulcerations ( ) Yes ( ) No

---

7. Neck (Especially thyroid gland): ( ) Normal ( ) Abnormal

Thyroid gland palpable	( )	Parotid gland enlargement	Right ( )	Left ( )
Enlarged	( )	Carotid pulse absent	Right ( )	Left ( )
Nodules	( )	Carotid bruit	Right ( )	Left ( )
Tenderness	( )			

Comment: ______________________

---

8. Thorax and Lungs: ( ) Normal ( ) Abnormal

( ) Asymmetrical expansion
( ) Hyperresonance
( ) Dullness
( ) Wheezes
( ) Rales

Describe any abnormality especially basilar rales:

____

____

____

Circumference at nipple level: Expiration _____ cm Inspiration _____ cm

9. Heart: ( ) Normal ( ) Abnormal

Displacement of apical impulse ( ) Yes ( ) No
Heart sounds normal ( ) Yes ( ) No ( ) S_1 ( ) S_2 ( ) S_3 ( ) S_4
Precordial thrust ( ) Yes ( ) No

Heart and Other Observations

Murmur ( ) No ( ) Yes

	Ao	Pu.	Apex	Mitral (lt.lat)
Sys	( )	( )	( )	( )
Dia	( )	( )	( )	( )

Describe any enlargement, irregularity of rate, murmurs, or thrills:

____

____

____

____

10. Abdomen: ( ) Normal ( ) Abnormal

Waist Measurement ________

( ) Heptomegaly

_____ cm. Liver span

( ) Spleenomegaly

Tenderness Liver ( )
Tenderness Spleen ( )
Tenderness Other ( )
Other mass: ( )

Describe any abnormality with special attention to the spleen and liver:

____

____

____

11. Extremities: ( ) Normal ( ) Abnormal

( ) Absence, specify: ______________

( ) Edema

Pitting ( ) Non-pitting ( )

( ) Clubbing of nails
( ) Varicosities
( ) Loss of hair on toes right
( ) Loss of hair on toes left

Describe any edema or signs of vascular insufficiency:

____

____

____

____

12. Peripheral Pulses	Normal	Dimin.	Absent	Comments:
Radial				
Femoral				
Popliteal				
Dorsalis Pedis				
Posterior Tibial				

13. Musculoskeletal: ( ) Normal ( ) Abnormal

MUSCLE

Weakness ( )
Tenderness ( )
Abnormal Consistency ( )
Atrophy ( )

Comments: ____________________

SPINE

Scoliosis ( )
Kyphosis ( )
Tenderness ( )
Tenderness level ________
Decreased range of motion ( )
Pelvic tilt ( )
Spine SLR RT ( )
Spine SLR LFT ( )

14. Genitourinary/Rectal/Hernia ( ) Normal ( ) Abnormal

( ) Inguinal hernia Rt.
( ) Inguinal hernia Lft.

( ) Varicocele
( ) Epididymis
( ) Scrotal mass

( ) Hemorrhoids
( ) Prostatic enlargement

	Absent	Enlarged	Atrophic
Testes Rt.	( )	( )	( )
Testes Lft.	( )	( )	( )

____ cm dia. ( ) Rectal mass

Comments: ____________________

15. Lymph Nodes (Check all areas) ( ) Normal ( ) Abnormal-Specify:

	Enlarged	Tender	Hard	Fixed	Confluent
Cervical	( )	( )	( )	( )	( )
Occipital	( )	( )	( )	( )	( )
Supraclavicular	( )	( )	( )	( )	( )
Axillary	( )	( )	( )	( )	( )
Epitrachlear	( )	( )	( )	( )	( )
Inguinal	( )	( )	( )	( )	( )
Femoral	( )	( )	( )	( )	( )

16. Nervous System - Separate Examination

17. Other Tests Ordered: ( ) Yes ( ) No

Tests ordered (Specify)

_______________ _______________

_______________ _______________

_______________ _______________

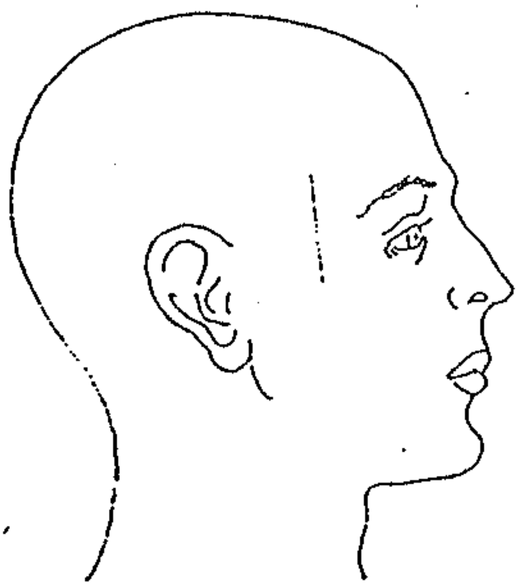
Signed: ______________________________
Examining Physician

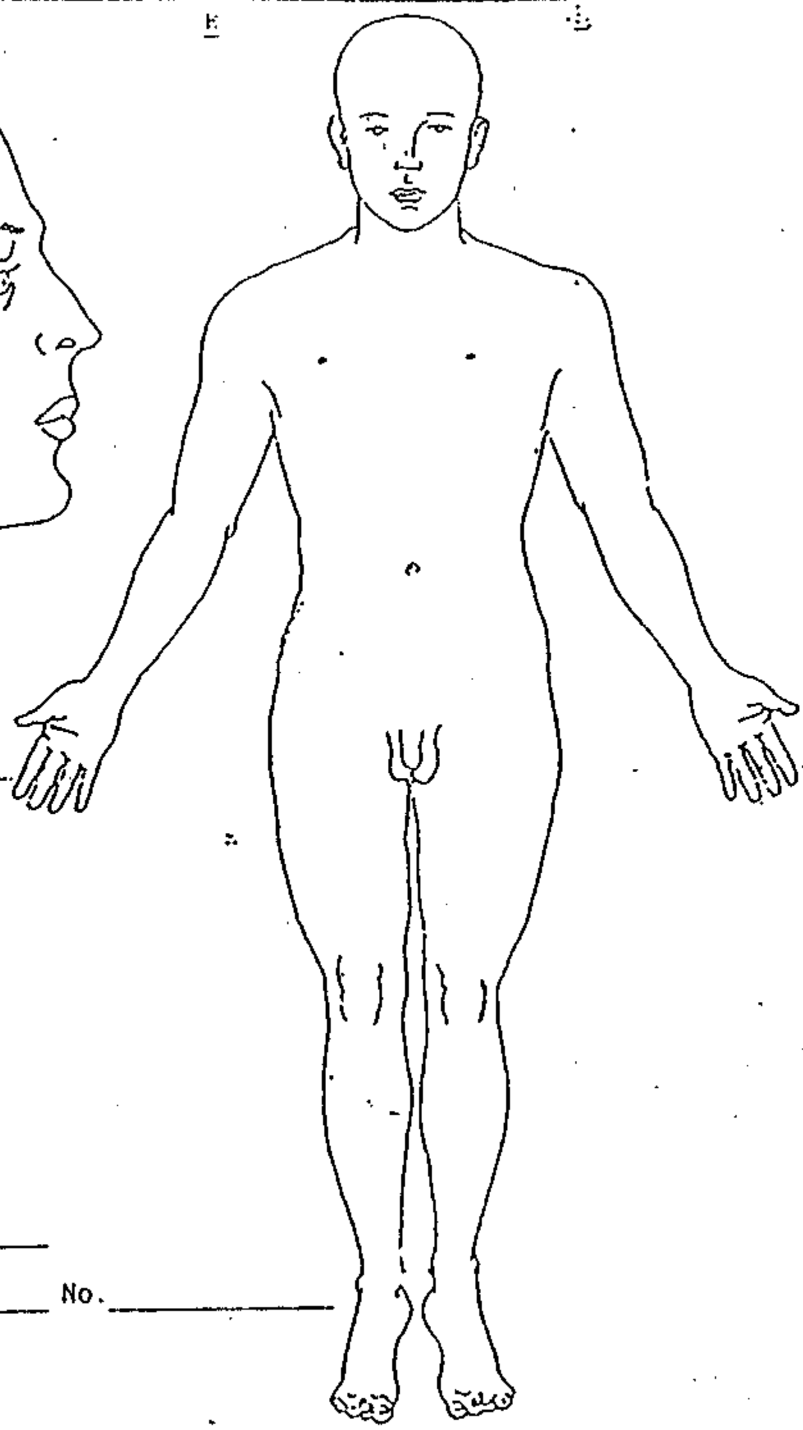
Examining Facility:

Printed Name of Examining Physician

Form 531 incl.

CLINICAL RECORD | ANATOMICAL FIGURE





NAME________________________

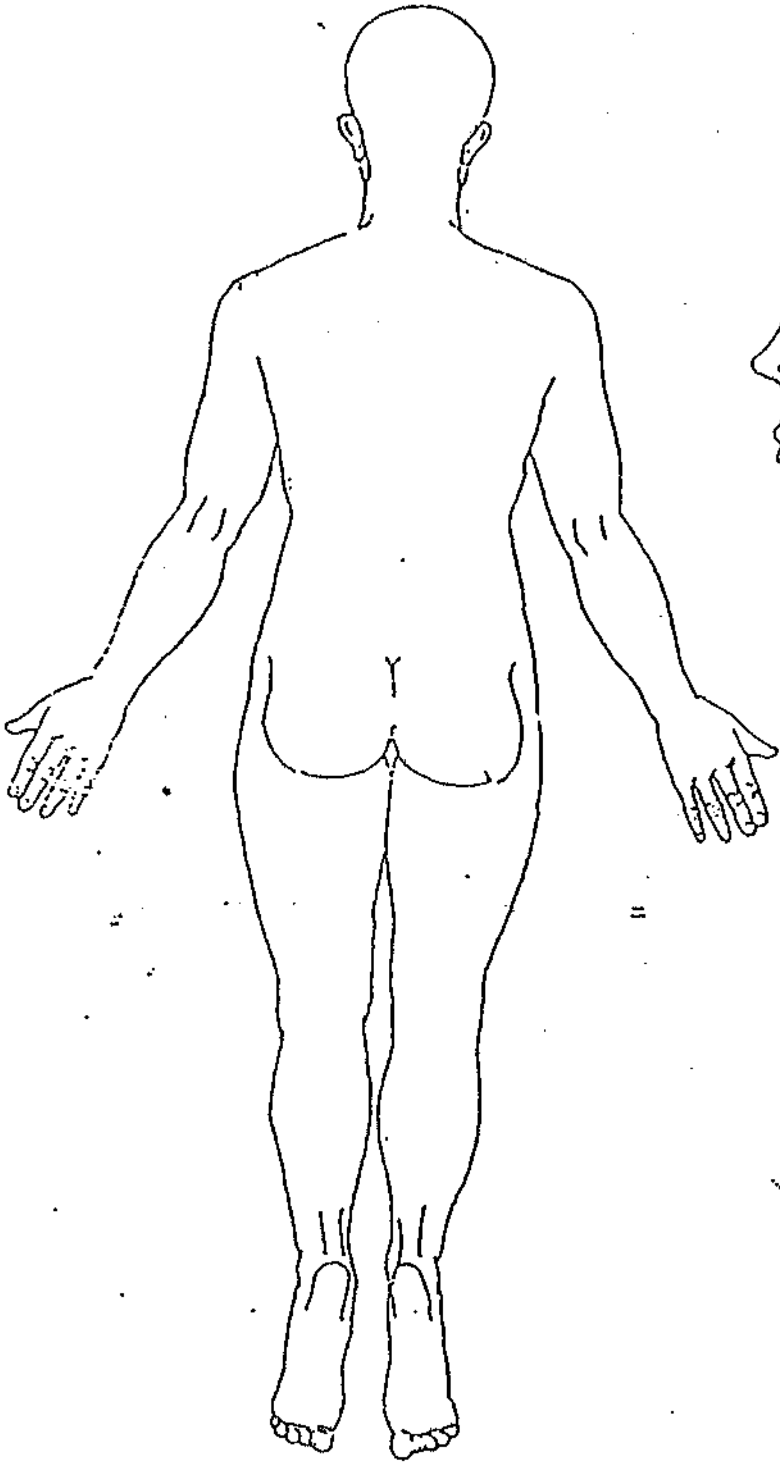
Date:________________________ No.______________

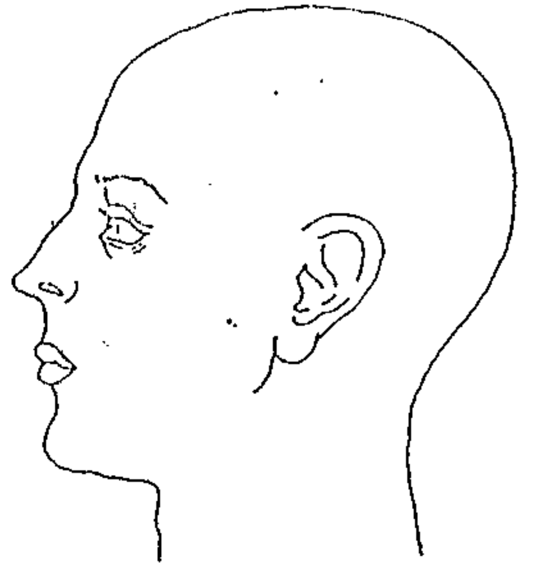
(Signed - Examiner)________________________

PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility) | REGISTER NO. | WARD NO.

ANATOMICAL FIGURE
Standard Form 53

Standard Form 53





Name:____________________ Date:_______________________ No.____________________

(Signed - Examiner)

SPECIALTY EXAMINATION - EXAMINER - (1 of 2)

NEUROLOGICAL EXAMINATION

NAME ______________________ DATE ______________________

CASE NO. ______________________

HEAD & NECK

	Yes	No
Normal to Palpations/Inspections	( )	( )

Specify: ( ) Scar
( ) Assemmetry
( ) Depression

	Yes	No
Neck Range of Motion - Normal	( )	( )

Decreased ( ) Left
( ) Right
( ) Forward
( ) Back

MOTOR SYSTEM

Handedness ( ) Right
( ) Left

	Yes	No
Gait - Normal or	( )	( )

( ) Broad Based
( ) Ataxic
( ) Small Stepped
( ) Other
Comments ______________________

____

MUSCLE STATUS (Strength, Tone, Volume, Tenderness, Fibrillations)

	Normal	Abnormal	Increased		Decreased	
			Right	Left	Right	Left
Rt. Arm Swing	( )	( )	( )	( )	( )	( )
Left Arm Swing	( )	( )	( )	( )	( )	( )
Muscle Bulk	( )	( )				
Tone - upper ext.	( )		( )	( )	( )	( )
Lower ext.	( )		( )	( )	( )	( )
Strength - Distal						
Wrist Extensors	( )		( )		( )	
Ankle/Toe Dors/. Flexors	( )				( )	( )
Proximal Deltoids	( )				( )	( )
Hip Flexors	( )				( )	( )

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	Yes	No
ABNORMAL MOVEMENTS (Tremors, Tics, choreas, etc)	( )	( )
Fasiculations If yes (1-4+) ________	( )	( )
Tenderness If yes, (1-4+) ________	( )	( )
Tremor (if yes, specify below)	( )	( )

	Resting	Essential	Intention	Other
Upper Extremities Rt.	( )	( )	( )	( )
Upper Extremities Lt.	( )	( )	( )	( )
Lower Extremities Rt.	( )	( )	( )	( )
Lower Extremities Lt.	( )	( )	( )	( )

COORDINATION	Normal	Abnormal
a. Equilibratory - Eyes Open		
Right Foot	( )	( )
Left Foot	( )	( )
Equilibratory - Eyes Closed		
Right Foot	( )	( )
Left Foot	( )	( )

b. Non-Equilibratory	Normal	Abnormal Rt.	Abnormal Left	Abnormal Both
Finger to Nose	( )	( )	( )	( )
Finger to Finger	( )	( )	( )	( )
Heel to Knee	( )	( )	( )	( )
Finger to Nose to Finger	( )	( )	( )	( )
Heel-Knee-Shin	( )	( )	( )	( )
c. Succession Movements (Including cheek, rebound posture-holding)	( )	( )	( )	( )
Rapidly Alternative Movements	( )	( )	( )	( )

SKILLED ACTS- PRAXIS	Normal	Abnormal
a. Handwriting (if indicated)	( )	( )
b. Speech (articulation, aphasia, agnosia) Grossly	( )	( )

if abnormal specify
( ) Dysarthia
( ) Aphasia

Reflexes (Code 0=absent, 1=sluggish, 2=active, 3=very active, 4=transient clonus, 5=sustained clonus, 6=other SPECIFY UNDER COMMENTS BELOW)

	Right	Left
Biceps	( )	( )
Triceps	( )	( )
Patellar	( )	( )
Achilles	( )	( )
Cremasteric	( )	( )
Abdominal	( )	( )
Abnormal Babinski Present? No ( ) Yes ( )	( )	( )

COMMENTS____

MENINGEAL IRRITATION

	Normal	Abnormal Rt.	Left	Both
Straight leg raising	( )	( )	( )	( )

SENSORY SYSTEM (tactile, pain vibration, position . If positive sensory signs are present summarize below and indicate details on Anatomical - Standard Form 531)

	Normal	Abnormal Rt.	Left	Both
Light Touch	( )		( )	
Pin Prick	( )		( )	
Vibration (@ ankle, 128hz Tuning Fork)	( )	( )	( )	( )
Position (Great Toe)	( )	( )	( )	( )

CRANIAL NERVES	Present	Absent
Right-smell	( )	( )
Left - smell	( )	( )

KS-AF-4 rev. I

	Normal	Abnormal
FUNDUS - Right:	( )	( )
If abnormal:		
( ) Disk Pollar Atrophy		
( ) Exudate		
( ) Papilledema		
( ) Hemorrhage		
Fundus - Left:	( )	( )
If abnormal:		
( ) Disk Pollar Atrophy		
( ) Exudate		
( ) Papilledema		
( ) Hemorrhage		
FIELDS - Right to confrontation	( )	( )
Fields - Left to confrontation	( )	( )

PUPILS

Size ________ mm ( ) equal ( ) unequal difference ________
Shape, position ( ) round ( ) other rt. ( ) other left
Light, reaction ( ) normal ( ) abnormal rt. ( ) abnormal left

Position of Eyeballs ( ) normal
( ) deviation medial rt. ( ) deviation lateral rt.
( ) deviation medial lt. ( ) deviation lateral lt
( ) deviation medial both ( ) deviation lateral both

Movements ( ) ( )
if abnormal describe ________________________________

____

NYSTAGMUS ( ) rotary ( ) horizontal ( ) vertical ( ) None

Draw position:

PTOSIS ( ) None ( ) right ( ) left

MOTOR

	Symmetric	Deviated Right	Deviated Left
Clench Jaw, rt.	( )	( )	( )
Clench Jaw, left	( )	( )	( )

SENSORY

	Normal	Abnormal V_1	Abnormal V_2	Abnormal V_3
Sensory right	( )	( )	( )	( )
Sensory left	( )	( )	( )	( )

CORNEAL REFLEX (✓) present right ( ) Absent Right
( ) present left ( ) Absent left

MOTOR RIGHT

	Yes	No
Normal Smile Rt.	( )	( )
Normal Smile Left	( )	( )

Palpebral Fissure ( ) Normal ( ) Abnormal

PALATE AND UVULA	Normal		Deviation
Movement	( )		Rt. ( ) Left ( )
Palatal Reflex Rt.	( ) normal		( ) abnormal
Palatal Reflex Left	( ) normal		( ) abnormal
Tongue-Protruded	( ) Central	( )Right	( ) Left
Atrophy	( ) No		( ) Yes

MENTAL STATUS (Alert, clear, cooperative, etc)

Gross abnormalities ( ) yes ( ) no

If yes, specify: ______________________

____

____

____

ADDITIONAL COMMENTS: ______________________

____

____

____

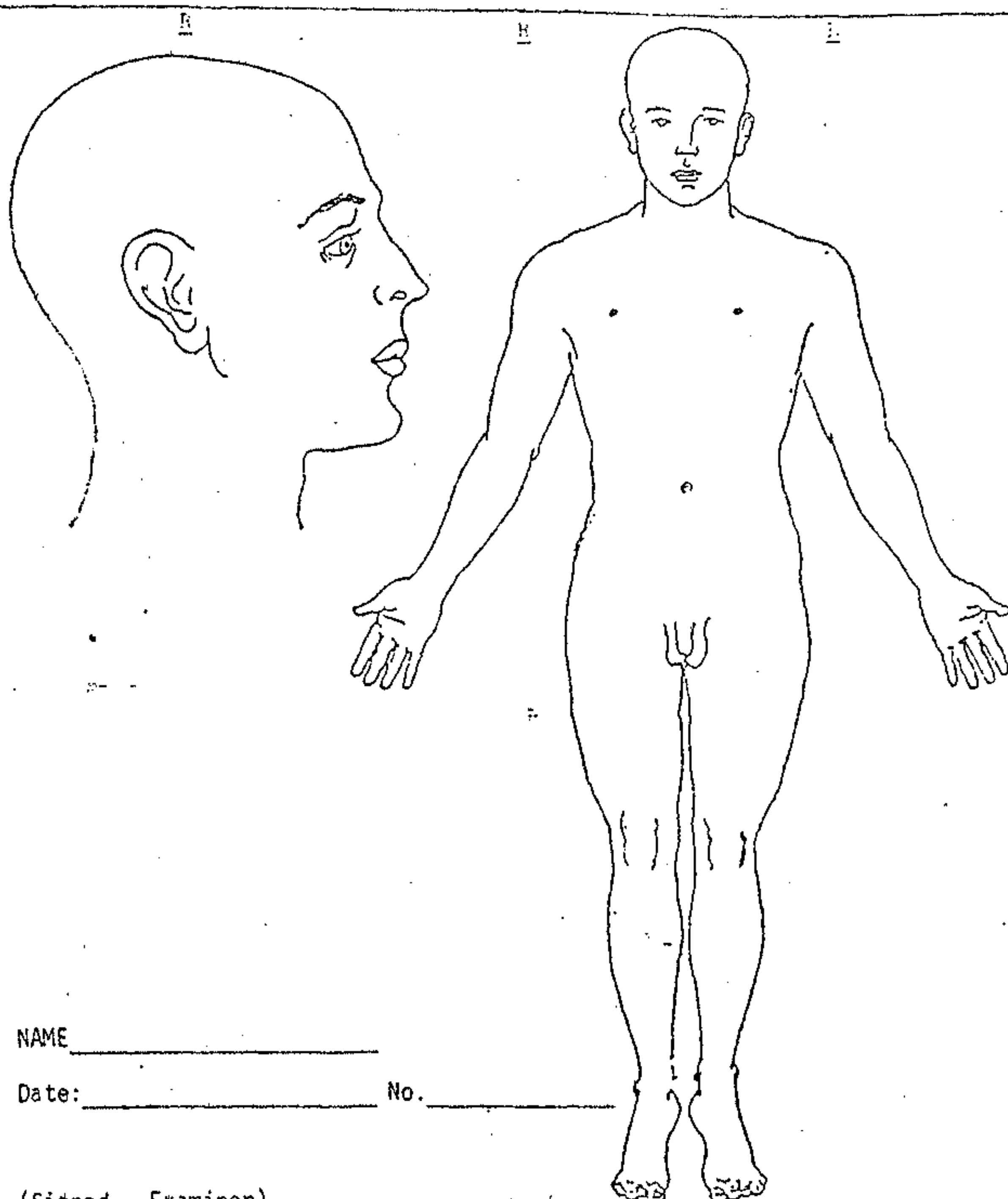
____

____

____

Signed ______________________
Examining Physician

CLINICAL RECORD | ANATOMICAL FIGURE



NAME____________________

Date:____________________ No.____________

(Signed - Examiner)____________________

PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility) | REGISTER NO. | WARD NO.

ANATOMICAL FIGURE
Standard Form 531

KS-AF-4

Standard Form 531

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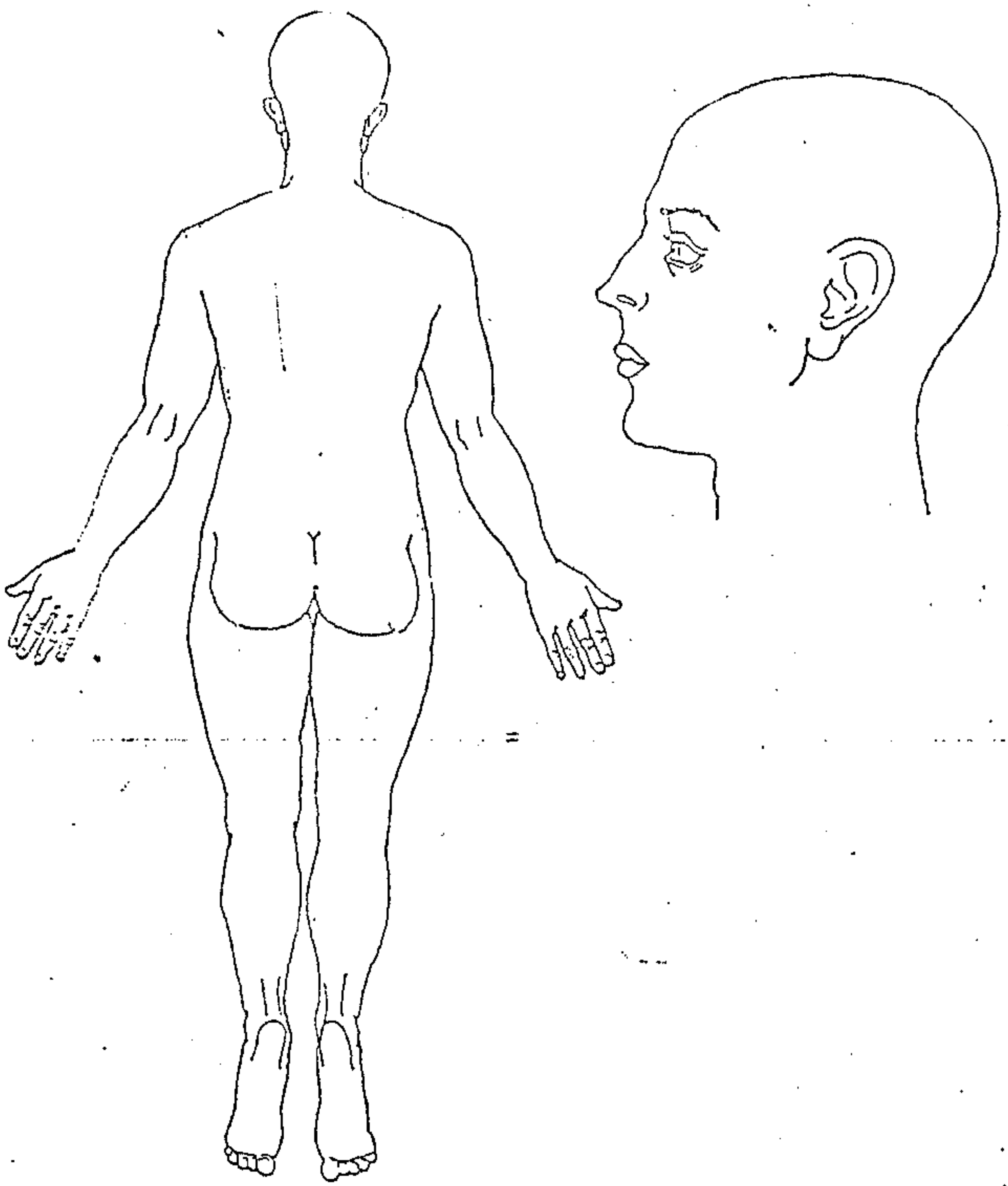


Name:________________ Date:________________ No.________________

(Signed - Examiner)

SPECIALTY EXAMINATION - NEUROLOGY - (1 of 2)

Standard Form 531

:IALTY EXAMINATION - DERMATOLO(

NAME____________ ___________

Date__________________________

No.___________________________

Skin:

Normal ( ) Abnormal ( ) - Indicate type and location of lesions on the anatomical figure - attached

( ) Comedones
( ) Acneiform lesions
( ) Acneiform Scars
( ) Depigmentation
( ) Inclusion Cysts
( ) Cutis Rhomboidalis
( ) Hyperpigmentation
( ) Jaundice
( ) Spider Angiomata
( ) Palmer Erythema

( ) Palmer Keratosis
( ) Petechiae
( ) Ecchymoses
( ) Conjunctiva
( ) Oral Mucosa
( ) Finger Nails
( ) Toe Nails
( ) Soles of Feet
( ) Dermatographia

****

Photographs taken? If so indicate areas photographed: (ONLY SUSPECT LESIONS)

( ) Face (right) ( ) Neck ( ) Chest

( ) Face (left) ( ) Shoulders ( ) Stomach

( ) Face (Full)

BIOPSY

( ) Skin Biopsy Performed (Check if yes) Consent Form obtained? Yes ( ) No ( )

________________________Biopsy location

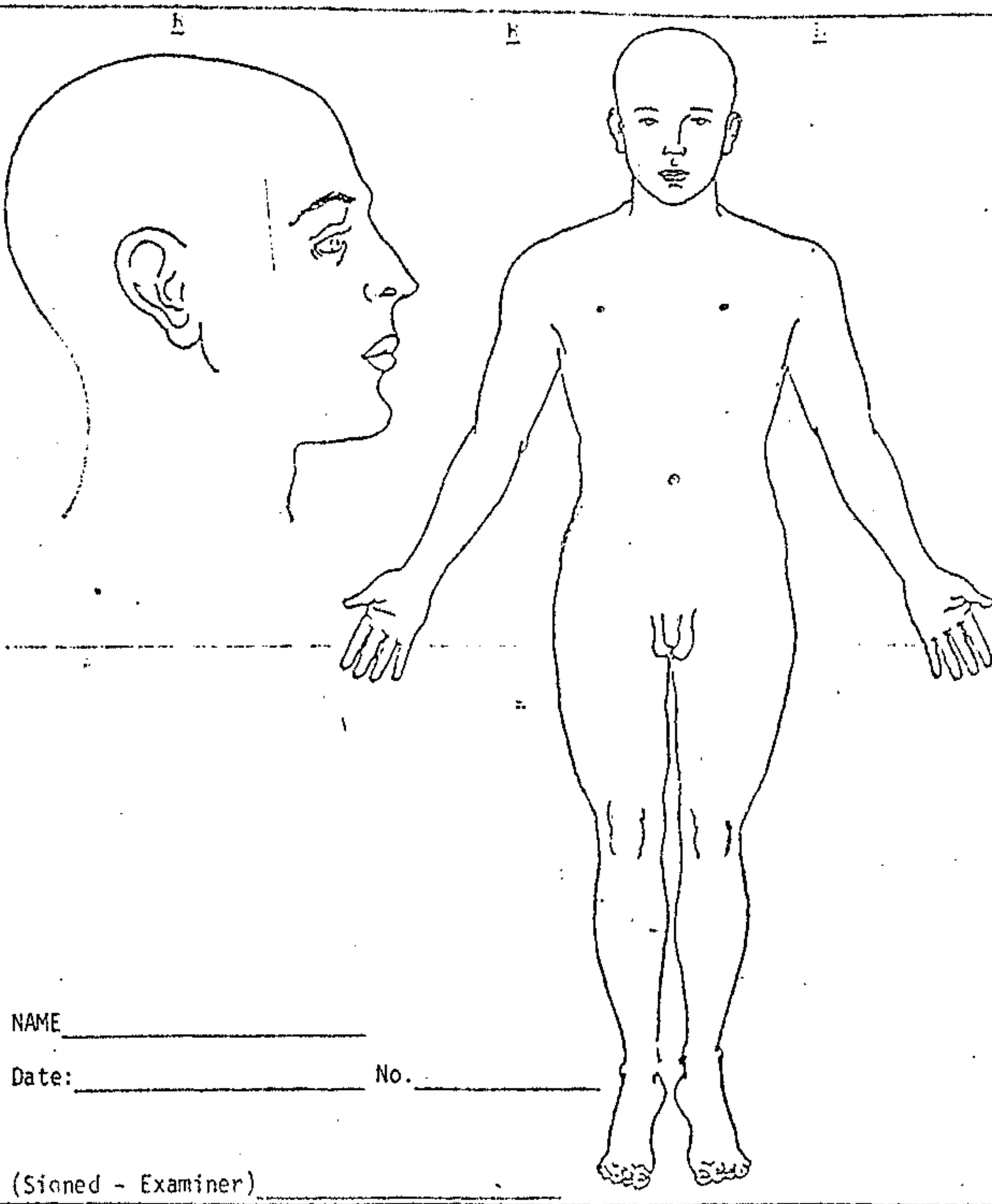
COMMENTS:____

____

____

Signed______________________________

CLINICAL RECORD | ANATOMICAL FIGURE



NAME________________________

Date:______________________ No.______________

(Signed - Examiner)______________________

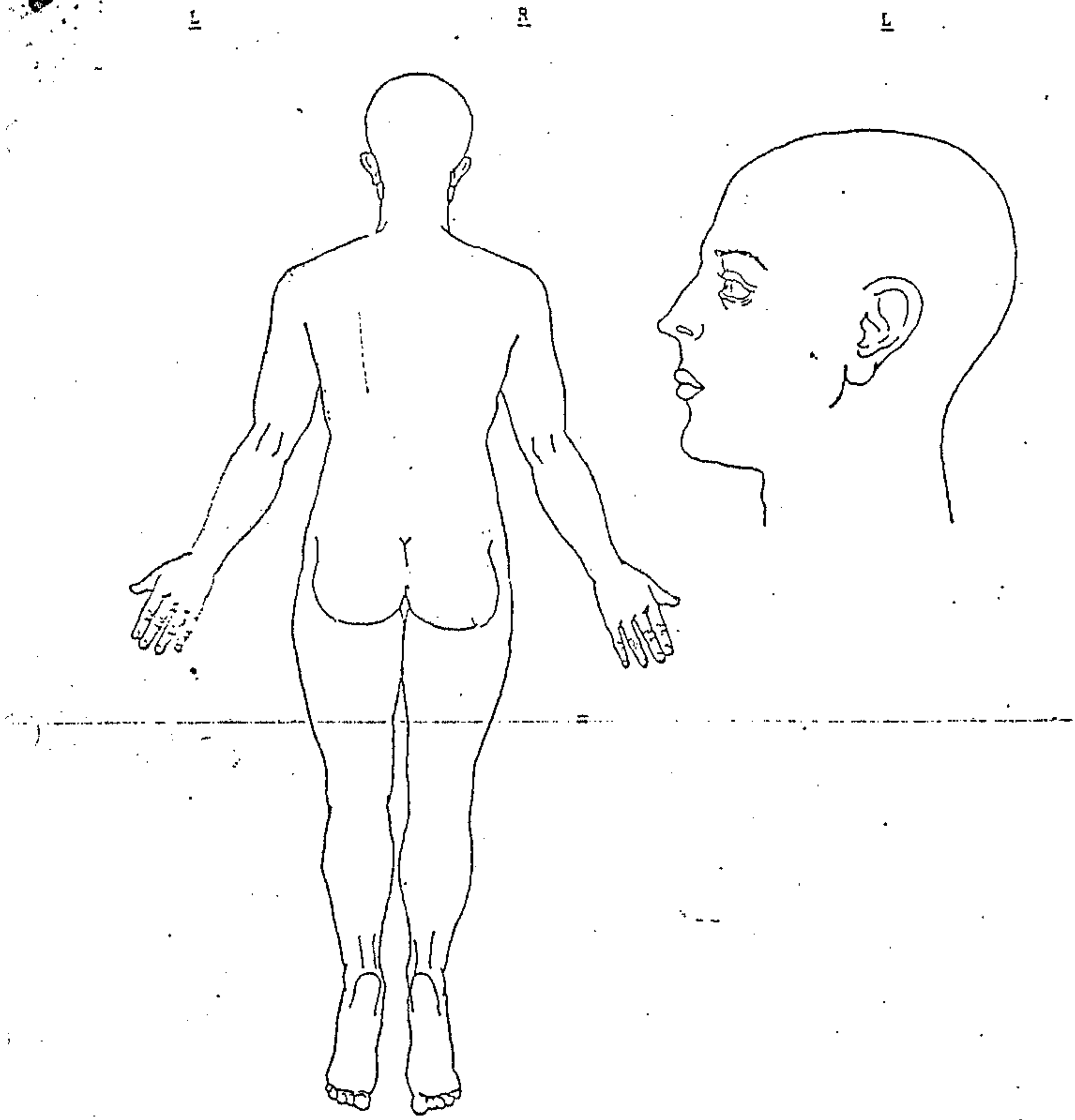
PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility)

REGISTER NO.	WARD NO.

ANATOMICAL FIGURE
Standard Form 531

Standard Form 531

KS-AF-2



Name:______________ Date:______________ No.______________

______________ (Signed - Examiner) ______________

U.S. GOVERNMENT PRINTING OFFICE

SPECIALTY EXAMINATION - DERMATOLOGY - ANATOMICAL FIGURE (1 of 2)

Standard Form 531

KS-AF-2

P U L M O N A R Y   F U N C T I O N

NAME______________________ Test Date________________

Age______________________

Case No.__________________

	Actual	Predicted	%
FVC	____________	________	______
FEV-1	____________	________	______
FEV-1/FVC	____________ %	________	______

*Comments regarding test performance:________________________________

____

____

Testing Technician______________

*complete only if performance is
questioned - i.e., cold, bronchitis, etc.

Equipment Used: Breon Spirometer

COMMENTS OF REVIEWING PHYSICIAN ________________________________

____

____

Signature______________________
Reviewing Physician

KS-AF-3 rev.

DATE:

NAME: NUMBER: AGE: TEMPERATURE:

NERVE	SITE	RECORD	GAIN	DISTANCE	STIM. CURR.	C.V.	LAT.	DIFF.
ULNAR	WRIST		5K	CM			.	
	BELOW ELBOW		5K	CM			.	
	ABOVE ELBOW		5K	CM			.	
PERONEAL	ANKLE		2K	CM			.	
	FIBULAR HEAD		2K	CM			.	
SURAL			10	14 CM			.	

COMMENTS:

AVT-27

NAME: ____________

DIAGNOSTIC SUMMARY

SYNOPSIS OF POSITIVE FINDINGS

Medical History:

1. ____________
2. ____________
3. ____________
4. ____________
5. ____________

PHYSICAL EXAMINATION (Complete below and continue on additional page - reference no.)

1. General ____________

2. Dermatologic ____________

3. Neurological Including Nerve Conduction Studies ____________

. Psychological (Bianary Provided) ____________

KS-AF-7

AVI-28

NAME: ______________________

DIAGNOSTIC SUMMARY

SYNOPSIS OF POSITIVE FINDINGS

Medical History: 1. ______

2. ______

3. ______

4. ______

5. ______

PHYSICAL EXAMINATION (Complete below and continue on additional page - reference no.)

1. General ______

2. Dermatologic ______

3. Neurological Including Nerve Conduction Studies ______

. Psychological (Bianary Provided) ______

Appendix VII

EXAMINATION PARAMETERS AND ABNORMALITY WEIGHTS
USED IN ASSESSING INDIVIDUAL HEALTH

Organ System	Parameter	Relative Weight Assigned to an Abnormality
Hematologic	RBC	2
	WBC	2
	Hemoglobin/Hematocrit	3
	RBC Indices (MCV/MCH/MCHC)	2
	Platelets	4
Cancer	Skin Cancer	3
	Systemic Cancer	10
Endocrine	T3	3
	T4	4
	FTI	3
	Glucose 2-hour Postprandial	6
	Testosterone	3
Pulmonary	FEV 1	4
	FVC	4
	FEV 1/FVC Ratio	4
	X-ray	8
Hepatic	Enzymes (SGOT, SGPT, GGTP, Alkaline Phosphatase)	3
	Total Bilirubin	3
	Direct Bilirubin	3
	LDH	3
	Cholesterol	4
	HDL	5
	Triglycerides	4
	Uroporphyrins	4
	Coproporphyrins	3
	ALA	3
	Hepatomegaly	6
Reproductive	Sperm Count	1
Psychological	MMPI (10 Major Scales)	4
	Halstead-Reitan	5
	IQ Scores (VRQ, PRQ, FLQ)	4

General Health	Examiner's Assessment	3
	Percent Body Fat	3
	Sedimentation Rate	2
Cardiovascular	Systolic Blood Pressure	7
	Diastolic Blood Pressure	8
	ECG	9
	Heart Sounds	7
	Eye Grounds	6
	Proximal Pulses (Carotid/Femoral)	5
	Distal Pulses (Popliteal/Dorsalis Pedis/Posterior Tibial)	4
Renal	BUN	5
	Occult Blood	2
	WBC in Urine	2
	Protein in Urine	4
	Specific Gravity	5
Dermatologic	Normal/Abnormal	1
Neurological	Smell (Bilateral)	1
	Visual Fields (Bilateral)	3
	Pupils (Reaction and Movement)	3
	Sensation/Corneal Reflex/Jaw Clench (Bilateral)	3
	Smile/Palpebral Fissure	3
	Palate Movement and Reflex/Neck Range of Motion	3
	Speech/Tongue Protrusion	3
	Pinprick/Light Touch/Vibration Sense	3
	Muscle Status	3
	Central Function (Finger-to-Nose/Romberg/Tremor/Gait)	3
	Babinski	4
	Tendon Reflexes (Patellar/Archilles/Biceps)	5
	Ulnar Velocities (Above and Below)	3
	Peroneal Velocities	3

Appendix VIII

TOTAL MORTALITY AND MORBIDITY STUDY
SITE SPECIFIC MALIGNANT NEOPLASMS

	Mortality		Morbidity			
		Comparison		Comparison		
Site ICD Code (9th Ed)	Ranch Hand	(First cohort only)	Ranch Hand	O	S	R
Lip, oral cavity, Pharynx (140-149)	0	1	4	2	0	0
Digestive organs, peritoneum (150-159)	0	1	0	4	0	1
Respiratory, intrathoracic (160-165)	2*	4*	2	1	0	0
Bone, connective tissue, skin, breast (170-175)	0	0	0	0	0	0
Genitourinary organs (179-189)	1	1	6	2	1	0
Brain (191-192)	0	1	1	0	0	0
Thyroid (193)	0	0	0	1	0	0
Lymphatic and hematopoietic tissue (200-208)	0	1	0	0	0	1
No site specification (199)	1	1	0	0	0	0
TOTAL	4	10	13	10	1	2

O = Original
S = Shifted
R = Replaced

*Includes 1 Ranch Hand and 1 comparison who expired following interview.

Appendix IX

GENERAL HEALTH ANALYSES USING DATA FROM ALL COMPARISONS

SELF-PERCEPTION OF HEALTH BY GROUP

Perception	Ranch Hand Number(%)	All Comparisons Number(%)
Excellent	392(38)	480(40)
Good	435(42)	523(44)
Fair	159(15)	143(12)
Poor	53(5)	46(4)
	1039	1192
		p=0.05

SELF-PERCEPTION OF HEALTH BY GROUP MEMBERSHIP AND OCCUPATIONAL CATEGORY

Occupational Group	Perception of Health: Excellent	Good	Fair/Poor	p value
Officer, flying				
Ranch Hand	198	121	42	0.66
Comparison	225	145	40	
Enlisted, flying				
Ranch Hand	59	83	42	0.97
Comparison	65	89	43	
Enlisted, ground				
Ranch Hand	126	225	127	0.005
Comparison	176	280	103	

DISTRIBUTION OF BODY FAT (PERCENT)

	Lean <10%)	Normal (10-25%)	Obese (>25%)
Ranch Hand	13	824	208
Comparison	12	961	247

P = 0.83

PERCENTILE DISTRIBUTION OF SEDIMENTATION RATE RESULTS

	5%	25%	50%	75%	95%
Ranch Hand	0	1	2	4	12
Comparison	0	1	2	4	12

Appendix X

FERTILITY AND REPRODUCTIVE ANALYSES;
RANCH HANDERS VERSUS ALL COMPARISONS

ANALYSES OF CONCEPTION OUTCOMES, UNADJUSTED FOR MATERNAL COVARIABLES (COMPLETE AND PARTIAL DATA SUBSETS);
RANCH HANDERS VERSUS ALL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Miscarriage						
Ranch Hand	295	(14.4)	1754	190	(16.0)	1001
Comparison	282	(11.9)	2089	233	(14.0)	1430
		P = 0.01			P = 0.15	
Stillbirth						
Ranch Hand	13	(0.6)	2036	16	(1.3)	1175
Comparison	21	(0.9)	2350	12	(0.7)	1651
		P = 0.34			P = 0.10	
Induced Abortion						
Ranch Hand	13	(0.6)	2036	62	(5.2)	1129
Comparison	18	(0.8)	2353	65	(6.0)	1563
		P = 0.62			P = 0.36	
Live Birth						
Ranch Hand	1723	(84.1)	326	917	(77.0)	274
Comparison	2042	(86.1)	329	1309	(78.7)	354
		P = 0.06			P = 0.27	

CONCEPTION OUTCOMES (COMPLETE DATA SUBSET)
BY GROUP MEMBERSHIP AND TIME;
RANCH HANDERS VERSUS ALL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Miscarriage						
Ranch Hand	239	(13.7)	1505	156	(15.0)	883
Comparison	233	(11.6)	1776	188	(13.2)	1238
		P = 0.05			P = 0.20	
Stillbirth						
Ranch Hand	9	(0.5)	1735	12	(1.2)	1027
Comparison	13	(0.6)	1996	12	(0.8)	1414
		P = 0.60			P = 0.43	
Induced Abortion						
Ranch Hand	8	(0.5)	1736	37	(3.6)	1002
Comparison	8	(0.4)	2001	53	(3.7)	1373
		P = 0.76			P = 0.84	
Live Birth						
Ranch Hand	1487	(85.3)	257	833	(80.2)	206
Comparison	1752	(87.2)	257	1170	(82.0)	256
		P = 0.08			P = 0.24	

RESULTS OF THE ANALYSIS OF CONCEPTION OUTCOMES
RANCH HANDERS VERSUS ALL COMPARISONS

Relationship	P value
Miscarriage by Group by Pre/Post-SEA	0.70
Stillbirth by Group by Pre/Post-SEA	1.00
Induced Abortion by Group by Pre/Post-SEA	1.00
Live Birth by Group by Pre/Post-SEA	0.78

ANALYSES OF LIVE BIRTH OUTCOMES, UNADJUSTED FOR MATERNAL COVARIABLES (COMPLETE AND PARTIAL DATA SUBSETS); RANCH HANDERS VERSUS ALL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Learning Disability						
Ranch Hand	61	(3.5)	1662	77	(8.4)	840
Comparison	81	(8.0)	1961	81	(6.2)	1228
		P = 0.49			P = 0.05	
Physical Handicaps						
Ranch Hand	144	(8.4)	1579	132	(14.4)	785
Comparison	176	(8.6)	1866	130	(9.9)	1179
		P = 0.77			P = <0.01	
Infant Death						
Ranch Hand	8	(0.5)	1715	4	(0.4)	913
Comparison	4	(0.2)	2038	3	(0.2)	1306
		P = 0.15			P = 0.39	
Birth Defects						
Ranch Hand	90	(5.2)	1633	80	(8.7)	837
Comparison	123	(6.0)	1919	84	(6.4)	1225
		P = 0.29			P = 0.04	
Neonatal Death						
Ranch Hand	25	(1.5)	1698	14	(1.5)	903
Comparison	28	(1.4)	2014	3	(0.4)	1305
		P = 0.84			P = <0.01	

LIVE BIRTH OUTCOMES (COMPLETE DATA SUBSET); RANCH HANDERS VERSUS ALL COMPARISONS

	Pre-SEA			Post-SEA		
	Yes	(%)	No	Yes	(%)	No
Learning Disability						
Ranch Hand	57	(3.8)	1430	75	(9.0)	758
Comparison	72	(4.1)	1680	74	(6.3)	1096
Physical Handicap						
Ranch Hand	134	(9.0)	1353	126	(15.1)	707
Comparison	160	(9.1)	1592	118	(10.1)	1052
Infant Death						
Ranch Hand	7	(0.5)	1480	3	(0.4)	830
Comparison	3	(0.2)	1749	1	(0.1)	1169
Birth Defects						
Ranch Hand	78	(5.2)	1409	76	(9.1)	757
Comparison	113	(6.4)	1639	77	(6.6)	1093
Neonatal Death						
Ranch Hand	20	(1.3)	1467	14	(1.7)	819
Comparison	28	(1.6)	1724	4	(0.3)	1166

RESULTS OF THE ANALYSIS OF LIVE BIRTH OUTCOMES; RANCH HANDERS VERSUS ALL COMPARISON

Relationship	P Value
Learning Disability by Group by Pre-Post SEA	0.12
Physical Handicap by Group by Pre-Post SEA	0.02
Infant Death by Group by Pre-Post SEA	1.0
Birth Defects by Group by Pre-Post SEA	0.02
Neonatal Death by Group by Pre-Post SEA	0.03

Appendix XI

INTRODUCTORY LETTERS

- Secretary of Air Force
- USAF Surgeon General with Fact Sheet

DEPARTMENT OF THE AIR FORCE
WASHINGTON, D C 20330

OFFICE OF THE SECRETARY

James W. Doe
1215 Middle Grove
Norfork, MD 23456

Dear Mr Doe

The Air Force will soon begin conducting a very comprehensive health assessment of certain Air Force members who served our Nation in the Vietnam conflict. This health assessment is part of a medical study designed to help determine if you or your fellow Vietnam veterans may have had any compromise to your health as a result of exposure to the complex environment of Southeast Asia.

Scientists at the USAF School of Aerospace Medicine have been given the responsibility for conducting this important project. The Air Force Surgeon General will contact you soon with more details and ask for your voluntary participation.

A major focus of the President's program for veterans is the resolution of health issues raised by them. The Air Force and I are committed to doing our part in resolving these issues. I ask that you help us and all Vietnam veterans by voluntarily participating in this major study.

Sincerely,

Verne Orr
Secretary of the Air Force

DEPARTMENT OF THE AIR FORCE
HEADQUARTERS UNITED STATES AIR FORCE
BOLLING AFB DC 20332

James W. Doe
1215 Middle Grove
Norfork, MD 23456

Dear Mr Doe

The Air Force is conducting a very comprehensive health assessment of certain Air Force members who served our Nation in the Vietnam conflict. The USAF School of Aerospace Medicine has been given the responsibility for conducting this study.

The purpose of the study is to determine whether there may be any causal relationship between health problems and exposure to the complex and unique environment of the war in Southeast Asia. Simply stated, we do not know if such health effects exist. You are being asked to voluntarily participate in this study because of your unique Southeast Asia experience. Your participation is critical to the success of this study. However, you should not view this invitation to participate as a cause for alarm nor as an implication that you are at risk for any known disease.

To insure the scientific validity of the study, both an in-depth interview and a detailed physical examination will be conducted. The administration of the interview will begin soon under the direction of a nationally recognized health survey organization. You will be contacted by phone or letter to arrange a convenient time for an in-home interview which will take from two to three hours.

Shortly after the interview you will again be contacted to schedule a physical examination at a nationally recognized civilian medical facility. The physical examination will take approximately four days. Every effort will be made to minimize disruption of your normal activities and to facilitate your participation in the study. Travel and per diem will be paid by the Air Force. For those not precluded by law, a stipend of $100 per day will be paid as a partial compensation for your time.

Our intent is to maintain all individual health data in strictest confidence. In case outside parties attempt to gain access to the data, the Air Force and the Department of Justice are committed to protect this individual confidentiality. Only in the event of an adverse final court decision, or in the highly unlikely instance where serious medical deficiencies must be shared with appropriate medical authorities to protect public health and safety, will any personal health data be revealed. You are referred to the Fact Sheet for further information regarding this matter.

This is perhaps one of the most important health studies undertaken by the Air Force. Your voluntary participation is critical to its success. Although you may feel healthy, numerous Vietnam veterans believe that they have illnesses which may be attributable to service in Southeast Asia. The only way we can get clarification of these difficult questions is through your cooperation and participation.

Sincerely

PAUL W. MYERS
Lieutenant General, USAF, MC
Surgeon General

1 Atch
Fact Sheet

FACT SHEET

INTRODUCTION

- The USAF School of Aerospace Medicine, Brooks AFB, Texas, is conducting the study.

- You are being invited to participate in this study because of your specific duties and period of assignment in Southeast Asia.

PURPOSE

- To determine whether there is a causal relationship between adverse health effects and exposure to the complex environment of Southeast Asia.

METHODS

- An in-depth health questionnaire will be administered to you by a member of a health evaluation team from Louis Harris and Associates, Inc.

- A complete profile of your current health will be obtained by a physical examination which will be conducted by a nationally recognized outpatient clinic.

- Follow-up abbreviated health questionnaires and physical examinations will be conducted at years 3, 5, 10, 15, and 20 of the study.

- Travel expenses (including board and lodging) for the physical examination will be paid by the Air Force.

- Stipend of $100 per day will be paid to study participants who are not on active duty, Government employed or otherwise precluded by law from receiving such a stipend.

- Confidentiality is to be maintained except in two cases:

- A judicial order to release personal medical data following an Air Force and Justice Department defended lawsuit.

- Serious medical findings which impact public health and safety. Two examples of situations in which public health and safety would raise the questions of disclosure are: a participatnt has typhoid fever, a participant who directly impacts the safety of others either in his profession, or as a volunteer, is found to have a serious nerve, heart or mental disorder. In this instance a committee composed of a physician (whose specialty is the area of the identified problem), a physician of your choice, a flight surgeon, a judge advocate (lawyer) and a representative from your field of expertise will be convened to review the medical findings. Before any disclosure is made to medical authorities, the committee must determine that the findings jeopardize the public health and safety.

BENEFITS TO YOU

- You will receive a complete health review and physical examination of top level executive calibre at no cost to yourself.

- You will be completely informed of all examination results.

- The information from this study will be provided to a physician of your choice if you so request.

- Questions concerning the study may be referred to the USAF School of Aerospace Medicine, Epidemiology Division, Brooks Air Force Base, Texas 78235, or by calling collect AC 512 536-3309.

- If you have recently changed your address or have an unlisted phone number, please advise the USAF School of Aerospace Medicine at the above address and phone number so that your records may be properly updated.

Appendix XII

OCCUPATIONAL CATEGORY AND RACE
OF THE FULLY COMPLIANT POPULATION IN PERCENT AND COUNTS

Occupation Code		Ranch Hand		Comparisons					
				Original		Shifted		Replaced	
		%	Counts	%	Counts	%	Counts	%	Counts
Non-Black									
1	Officer-Pilot	82	278	71	218	78	32	59	94
2	Officer-Navigator	96	76	81	58	100	6	71	12
3	Officer-Other	83	20	77	10	67	8	100	7
	Officer Subtotal	85	374	73	286	78	46	61	113
4	Enlisted-Flt Eng	93	172	84	141	94	17	70	26
5	Enlisted-Other	86	436	75	301	75	91	75	133
	Enlisted Subtotal	88	608	77	442	77	108	74	159
	Total Non-Black	87	982	76	728	77	154	68	272
Black									
1	Officer-Pilot	67	4	80	4	-	0*	-	*
2	Officer-Navigator	100	2	100	2	-	0*	-	*
3	Officer-Other	0	0	100	1	-	0*	-	*
	Officer Subtotal	67	6	88	7	-	0*	-	*
4	Enlisted-Flt Eng	93	13	67	10	-	0	83	5
5	Enlisted-Other	90	44	76	28	69	9	55	11
	Enlisted Subtotal	90	57	73	38	69	9	62	16
	Total Black	88	63	75	45	69	9	62	16
Entire Population		87	1045	76	773	77	163	68	288

Appendix XIII

SELF-REPORTED REASONS FOR NONCOMPLIANCE TO QUESTIONNAIRE

Reason	Ranch Hand	Original	Shifted	Replaced	Total
Fear of Physical	-	2 (3%)	-	-	2 (2%)
Job Commitment	-	2 (3%)	-	12 (24%)	14 (11%)
Dissatisfaction with the Military	3 (9%)	9 (13)	1 (8%)	1 (2%)	11 (8%)
No Time - No Interest	23 (68%)	36 (51%)	9 (75%)	15 (29%)	60 (45%)
No Travel, Distance, Family	-	-	-	-	-
Confidentiality/ Active Duty	2 (5%)	10 (14%)	-	12 (24%)	22 (17%)
Health Reasons	0	-	-	1 (2%)	1 (1%)
Passive Refusals*	6 (18%)	11 (16%)	2 (16%)	10 (20%)	23 (17%)
TOTAL	34	70	12	51	133

*Unresponsive to scheduling attempts.

Appendix XIV

SELF-REPORTED REASONS FOR NONCOMPLIANCE TO PHYSICAL EXAMINATION

Reason	Ranch Hand	Original	Shifted	Replaced	Total
Fear of Physical	6 (5%)	3 (2%)	-	3 (4%)	6 (2%)
Job Commitment	29 (24%)	51 (29%)	10 (27%)	20 (24%)	81 (27%)
Dissatisfaction With the Military	5 (4%)	-	-	-	0
No Time - No Interest	53 (43%)	94 (53%)	17 (46%)	43 (52%)	154 (52%)
No Travel-Distance Family	4 (4%)	10 (5%)	4 (11%)	7 (9%)	21 (7%)
Confidentiality-Active Duty	11 (9%)	8 (4%)	2 (5%)	6 (7%)	16 (5%)
Health Reasons	5 (4%)	3 (2%)	1 (3%)	1 (1%)	5 (2%)
Passive Refusals*	9 (7%)	10 (5%)	3 (8%)	2 (3%)	15 (5%)
	122	179	37	82	298

*Unresponsive to scheduling attempts.

Appendix XV

COEFFICIENT OF VARIATION FOR TRI-LEVEL CONTROLS

Control values were analyzed on 15 different laboratory tests for the period from January 14 thru December 13, 1982. Triplicate values were collected on each laboratory test at each of three different ranges (I, II, and III) except for triglyceride and alcohol which each had only ranges II & III. These control data were received from 91 groups of study participants reporting for physical examination (usually 2 groups per week). A total of 91 sets of control values were received for II & III and a total of 78 for I.

A one-way analysis of variance procedure was used on each trilevel laboratory test to determine whether or not the data varied significantly among the 91 (or 78) groups. The error term used was the pooled variance ($\hat{\sigma}_c^2$) from the triplicate values recorded for each group. The group means differed significantly at the 0.01 level on nearly all of the analyses (40 out of 42). Hence, the variability among the groups was significantly more than can be explained by the variability among the triplicate readings.

A variance component for the group-to-group variability ($\hat{\sigma}_g^2$) was estimated from the one-way analysis of variance and the standard deviation of a single measurement/group was estimated as:

$$\sigma = \sqrt{\hat{\sigma}_e^2 + \hat{\sigma}_g^2}$$

Each coefficient of variation given in the table below was computed as:

$$CV\% = \frac{\hat{\sigma} \times 100}{\bar{x}}$$

where the $\bar{x}$ is the mean of the control values for each trilevel/laboratory test. Ninety-five percent confidence limits were computed as follows:

$$\sqrt{\frac{N(N-1)v^2}{x^2_{.025,N-1}\left[N+(N-1)v^2\right]}} \le \frac{\sigma}{\mu} \le \sqrt{\frac{N(N-1)v^2}{x^2_{.975,N-1}\left[N+N-1)v^2\right]}}$$

where v^2 is the square of the observed CV, N = 91 or 78 (depending on the trilevel of interest) and σ and μ are the population parameters associated with σ and $\bar{k}$ respectively.

The interval for the CV%'s marked with an asterisk in the table below did not contain the USAFSAM required CV%, implying that the estimated CV% differed significantly from the required at the 5% level. The estimate exceeded the required on 12 of the 40 trilevel sets. The average CV% was not tested.

SAMPLE MEAN, STANDARD DEVIATION AND COEFFICIENT OF VARIATION
FOR TRI-LEVEL CONTROLS USED FOR 15 BIOCHEMICAL ASSAYS

	I		II		III		I	II	III		USAFSAM Require- ment
Test	$\bar{x}$	σ*	$\bar{x}$	σ	$\bar{x}$	σ	CV%	CV%	CV%	Aver- age	CV%
BUN	6.6	0.296	16.6	0.415	45.9	0.702	4.50*	2.50*	1.53	2.84	2.00
Creati- nine	0.602	-	1.697	0.024	5.637	0.053	-	1.40	0.93	1.16	2.50
Glucose	49.4	0.719	100.2	1.408	212.6	1.457	1.46	1.41	0.69	1.19	3.50
Choles- terol	104.2	2.236	115.8	2.357	151.7	2.257	2.15*	2.04*	1.49	1.89	1.50
Triglyc- erides	-	-	72.39	1.869	177.4	2.464	-	2.58*	1.39	1.98	2.10
HDL	20.5	1.111	31.6	0.786	37.8	1.535	5.42*	2.48	4.06*	3.99	3.50
Total Bili- rubin	0.930	0.040	1.437	0.045	5.470	0.133	4.34*	3.12*	2.42*	3.29	1.50
Conju- gated Bili- rubin	0.400	0.043	0.811	0.043	2.383	0.110	10.74*	5.33	4.60	6.89	6.00
Alk Phos	5.274	0.203	9.855	0.273	28.37	.438	3.85*	2.77	1.54	2.72	2.70
SGOT	38.32	1.18	56.73	1.41	171.2	2.18	3.08	2.48	1.27	2.28	4.00
SGPT	28.16	2.697	26.65	0.999	101.6	1.133	2.70	3.75	1.12	2.52	5.00
GGPT	31.97	0.985	43.68	1.033	186.79	2.20	3.08	2.37	1.18	2.21	5.00
LDH	147.9	1.997	165.8	2.612	441.7	4.104	1.35	1.57	0.93	1.28	2.20
CPK	65.5	1.362	139.1	5.559	440.9	11.34	2.08	4.00	2.57	2.88	5.00
Alco- hol	-	-	48.5	0.749	99.2	1.518	-	1.54	1.53	1.54	-

*P<0.05, reject the hypothesis that the sample CV% came from the population with required CV%

Appendix XVI

SPECIFIC RULES FOR ENTRY INTO THE MORBIDITY STUDY

CIRCUMSTANCES	RULES
Ranch Hander (RH) Dies Following Initial Data Collection	Control Followed Throughout and Replaced as Necessary
RH Dies of Combat Cause	Medical Records Reviewed; No Control Set Formed
RH Dies of Noncombat Cause Prior to Initial Data Collection	1st Order Surrogate Interview Accomplished; Control Selected and Followed Throughout; as Necessary
RH Noncompliant for Baseline Questionnaire and Physical	Control Followed Throughout the Study; Replaced as Necessary
RH Compliant for Questionnaire Noncompliant for Baseline Physical Examination	Control Followed Throughout the Study; Replaced as Necessary
RH Noncompliant During Follow-up	Control Followed Throughout the Study; Replaced as Necessary
Control Dies Following Initial Data Collection	Not Replaced in the Prospective Study of Morbidity
Control Dies of Combat Cause	Medical Records Reviewed; Excluded from Further Study
Control Dies of Noncombat Cause Prior to Initial Data Collection	Included in Mortality and Retrospective Morbidity Studies; Surrogate Interview Accomplished. Not Included in Prospective Morbidity Study and Replaced by a Living Compliant Control.
Control Noncompliant for Baseline Physical Examination	Control Followed Throughout Study Replace as Necessary
Control Noncompliant During Follow-up	Control Followed Throughout Study Replace as Necessary
Noncompliant Control Returns to Study	Both Primary and Replacement Controls will be Continued in Study

Appendix XVII

PERCENT COMPLIANCE BY FLYING CODE
AND MILITARY STATUS OF THE RANCH HAND
AND COMPARISON POPULATION NON-BLACK OFFICERS

Military Status** and Flying Code*	Participation: Fully Compliant	Partially Compliant	Non-Compliant	Total
Ranch Hand				
AF	77.4	19.4	3.2	100
RF	86.2	10.3	3.5	100
SVF	51.9	36.5	11.6	100
AN	96.2	3.8	0.0	100
RN	93.5	4.8	1.6	100
SVN	87.0	11.1	1.9	100
TOTAL	84.7	12.1	3.2	100
Comparison Original				
AF	58.9	32.2	8.9	100
RF	86.0	14.0	0.0	100
SVF	39.3	21.4	39.3	100
AN	75.0	15.0	10.0	100
RN	86.6	11.1	2.3	100
SVN	62.9	28.6	8.5	100
TOTAL	72.9	17.8	9.3	100
Comparison Shifted				
AF	87.5	0.0	12.5	100
RF	100.0	0.0	0.0	100
SVF	37.5	62.5	0.0	100
AN	75.0	25.0	0.0	100
RN	96.0	0.0	4.0	100
SVN	61.5	38.5	0.0	100
TOTAL	78.0	18.6	3.4	100
Comparison Replaced				
AF	57.9	34.2	7.9	100
RF	83.3	16.7	0.0	100
SVF	32.4	24.3	43.3	100
AN	88.9	0.0	11.1	100
RN	77.1	12.5	10.4	100
SVN	63.0	19.6	17.4	100
TOTAL	61.4	20.7	17.9	100

*F = Flying
*N = Nonflying
**A = Active
**R = Retired
**SV = Separated/Reserve

Appendix XVIII

RELATIVE RISKS FOR SELECTED CLINICAL END POINTS

CLINICAL PARAMETERS	Percent* RH	C	Relative Risk	95% Confidential Interval Exact	Normal Approx
Self Perception of Poorer Health ≤40 yrs	19.3	10.6	1.82	(1.18,2.10)	(1.17,2.87)
Self Perception of Poorer Health >40 yrs	21.4	15.8	1.35	(1.05,1.76)	(1.05,1.75)
Older Than Stated Age	0.8	0.1	5.92	(.80,262.37)	(.76,126.11)
Lean by Body Fat	1.2	0.9	1.37	(.51,4.043)	(.51,3.78)
Obese by Body Fat	19.8	20.3	0.97	(.80,1.18)	(.80,1.18)
Sed Rate ≤40	0.5	4.2	0.13		
Sed Rate >40	5.8	5.4	1.07	(.66,1.78)	(.66,1.77)
Skin Cancer	3.35	1.42	2.35	(1.18,5.11)	(1.16,4.90)
Systemic Cancer	1.24	1.03	1.20	(.46,3.33)	(.47,3.15)
Childless Marriages	20.9	19.5	1.07	(.93,1.23)	(.93,1.23)
Not Having Desired Children	18.3	19.9	0.92	(.76,1.10)	(.76,1.10)
Abnormal Sperm	4.6	4.6	0.99	(.54,1.86)	(.54,1.83)
Miscarriage	15.9	13.6	1.17	(.95,1.45)	(.95,1.45)
Stillbirth	1.3	0.8	1.60	(.65,4.30)	(.65,4.06)
Induced Abortion	5.2	6.8	0.76	(.54,1.087)	(.54,1.09)
Non-live Birth	23.0	22.1	1.04	(.89,1.22)	(.88,1.22)
Learning Disability	8.4	6.9	1.22	(.86,1.75)	(.86,1.75)
Physical Handicaps	13.8	11.4	1.21	(.93,1.58)	(.93,1.58)
Infant Death	0.5	0.4	1.35	(.26,8.67)	(.28,7.09)
Birth Defects	8.7	6.5	1.35	(.94,1.95)	(.95,1.94)
Neonatal Death	1.5	0.4	3.78	(1.06,20.45)	(1.03,16.50)
Reported Neuro Disease	4.59	5.18	.89	(.58,1.37)	(.58,1.37)
Smell, Left	1.82	1.56	1.17	(.54,2.63)	(.55,2.55)
Smell, Right	1.63	1.43	1.14	(.51,2.68)	(.51,2.59)
Visual Fields, Left	0.29	.26	1.12	(.13,13.28)	(.15,9.46)
Visual Fields, Right	0.19	.39	.49	(.041,4.31)	(.06,3.60)
Light Reaction	0.77	.52	1.48	(.40,6.68)	(.41,5.80)
Ocular Movement	34.8	35.3	.99	(.86,1.12)	(.86,1.13)
Sensation, Left	.67	.52	1.29	(.33,6.03)	(.34,5.25)
Sensation, Right	.38	.39	.99	(.17,6.74)	(.19,5.54)
Corneal Reflex	.19	.13	1.48	(.077,87.25)	(.11,41.17)
Jaw Clench	.096	0			
Smile	.38	.26	1.48	(.21,16.35)	(.24,11.59)
Palpebral Fissure	5.65	5.43	1.04	(.70,1.57)	(.70,1.56)
Balance	19.9	19.5	1.04	(.86,1.27)	(.86,1.26)
Gag Reflex	1.44	1.68	.86	(.38,1.94)	(.39,1.89)
Speech	.28	0			
Tongue in Midline	.45	.30	1.50	(.22,16.60)	(.24,11.78)
Palate and Uvula	.29	.13	2.22	(.18,116.45)	(.21,55.29)
Neck Motion	3.92	3.23	1.21	(.73,2.06)	(.73,2.04)
Pin Prick	9.41	9.56	.98	(.73,1.33)	(.73,1.33)

*Categorical values displayed as % abnormal with relative risk.

Appendix XVIII (Cont)

RELATIVE RISKS FOR SELECTED CLINICAL END POINTS

CLINICAL PARAMETERS	Percent* RH	C	Relative Risk	95% Confidential Interval Exact	Normal Approx
Light Touch	7.08	7.46	.95	(.67,1.35)	(.67,1.35)
Muscle Status	3.56	3.62	.98	(.59,1.65)	(.59,1.64)
Vibration	7.56	8.76	.86	(.62,1.20)	(.62,1.20)
Patellar Reflex	0.385	0.649	.59	(.12,2.75)	(.14,2.53)
Achilles Reflex	3.77	3.37	1.12	(.67,1.90)	(.67,1.88)
Biceps Reflex	0.771	0.519	1.49	(.40,6.72)	(.41,5.84)
Babinski	0.871	0.259	3.36	(.70,31.96)	(.69,22.50)
Tremor	5.29	4.01	1.32	(.84,2.10)	(.84,2.08)
Coordination	4.62	3.88	1.89	(.75,1.93)	(.74,1.91)
Romberg	19.9	19.2	1.04	(.86,1.26)	(.86,1.26)
Gait	2.31	1.83	1.27	(.64,2.65)	(.64,2.58)
Psychological Illness	3.45	2.07	1.67	(.91,3.20)	(.90,3.12)
Isolation (≥14)	4.62	2.34	1.97	(1.14,3.58)	(1.13,3.50)
Halstead-Reitan	33.5	33.5	1.00	(.85,1.17)	(.86,1.17)
SGOT	13.9	14.8	.93	(.74,1.18)	(.74,1.18)
SGPT	7.8	8.6	.91	(.66,1.26)	(.66,1.26)
GGPT	10.8	10.3	1.053	(.79,1.40)	(.79,1.40)
Alk Phos	17.3	16.9	1.020	(.83,1.26)	(.83,1.26)
T Bili	1.8	2.0	.90	(.43,1.90)	(.44,1.87)
D Bili	29.0	29.7	.98	(.84,1.13)	(.84,1.13)
LDH	1.7	2.1	.80	(.38,1.67)	(.39,1.65)
Chol	26.0	27.7	.94	(.80,1.10)	(.80,1.097)
Trig	34.7	36.1	.96	(.85,1.10)	(.85,1.097)
Uroporphyrins	6.5	6.8	.94	(.58,155)	(.58,1.54)
Coproporphyrins	0.2	0.0			
d-Aminolevulinic Acid	0.0	0.0			
Verified Hepatitis	3.83	4.14	.93	(.57,1.51)	(.57,1.50)
Jaundice	4.21	4.53	.93	(.59,1.48)	(.59,1.47)
Cirrhosis	.38	.39	.99	(.17,6.72)	(.19,5.52)
Other Hepatic Verified	1.53	.39	3.93	(1.13,21.07)	(1.09,16.99)
Reported Hepatomegaley	1.75	1.71	1.02	(.48,2.26)	(.48,2.20)
Observed Hepatomegaley	1.56	0.78	2.00	(.75,6.21)	(.74,5.69)
Skin Patches, etc., Reported	44.2	36.0	1.23	(1.09,1.40)	(1.09,1.39)
Reported Acne (Post SEA)	17.3	14.7	1.18	(.67,2.18)	(.67,2.15)
Reported Acne Severity	41.4	33.3	1.24	(.74,2.21)	(.74,2.20)
Reported Chloracne	36	45	.80	(.55,1.21)	(.55,1.21)
Comedones	21.7	20.7	1.050	(.87,1.26)	(.87,1.26)
Acneiform Lesions	18.3	17.5	1.047	(.85,1.29)	(.85,1.29)
Acneiform Scars	11.2	10.4	1.082	(.82,1.43)	(.82,1.43)
Cysts	11.6	10.5	1.11	(.84,1.46)	(.84,1.46)
Hyperpigmentation	8.3	7.1	1.17	(.84,1.65)	(.84,1.64)
Other Abnorms	12.6	16.3	.78	(.61,.98)	(.61,.98)
Any Abnormality	45.0	44.9	1.00	(.90,1.11)	(.90,1.11)

Appendix XVIII (Cont)

RELATIVE RISKS FOR SELECTED CLINICAL END POINTS

CLINICAL PARAMETERS	Percent* RH	C	Relative Risk	95% Confidential Interval Exact	Normal Approx
Systolic Blood Pressure <40 yrs	10.4	14.3	.73	(.46,1.18)	(.46,1.17)
Systolic Blood Pressure ≥40 yrs	23.1	24.6	.94	(.73,1.20)	(.73,1.20)
Diastolic Blood Pressure <40 yrs	5.2	5.4	.97	(.45,1.28)	(.46,2.12)
Diastolic Blood Pressure ≥40 yrs	11.6	13.9	.84	(.58,1.21)	(.58,1.21)
ECG Findings <40 yrs	20.1	23.1	.87	(.62,1.23)	(.62,1.22)
ECG Findings ≥40 yrs	30.2	28.4	1.061	(.86,1.32)	(.86,1.32)
ECG Δ <40 yrs	4.2	6.4	.66	(.05,8.73)	(.068,6.43)
ECG Δ ≥40 yrs	8.1	8.5	.95	(.49,1.88)	(.49,1.86)
Eye gnds <40 yrs	2.3	2.7	.86	(.27,2.97)	(.28,2.76)
Eye gnds ≤40 yrs	8.7	8.4	1.038	(.65,1.67)	(.65,1.66)
Peripheral Pulses	12.8	9.5	1.35	(.99,1.88)	(.99,1.88)
Reported Heart Disease	17.3	17.6	.98	(.80,1.21)	(.80,1.21)
Reported Heart Attack	.96	.52	1.85	(.54,8.05)	(.54,6.97)
Verified Heart Disease	14.06	14.10	1.00	(.79,1.27)	(.79,1.27)
Verified Heart Attack	.670	.390	1.73	(.40,10.32)	(.41,8.39)
RBC	7.43	6.28	1.18	(.82,1.71)	(.82,1.71)
WBC	12.45	11.65	1.069	(.82,1.40)	(.82,1.39)
HGB	3.28	3.27	1.003	(.59,1.74)	(.59,1.72)
HCT	8.30	7.59	1.094	(.78,1.53)	(.78,1.53)
MCU	3.76	3.40	1.11	(.66,1.90)	(.66,1.86)
MCH	46.24	39.66	1.17	(1.043,1.30)	(1.043,1.31)
MCHC	9.46	10.47	.90	(.68,1.21)	(.68,1.21)
PLT	1.16	1.97	.59	(.25,1.34)	(.26,1.32)
Occult Blood in Urine	1.341	1.293	1.037	(.43,2.60)	(.44,2.50)
Protein in Urine	1.3	2.6	.50	(.24,1.07)	(.25,1.067)
Reported Kidney Disease	5.6	3.5	1.60	(1.00,2.59)	(1.00,2.56)
T3↑	.87	.26	3.34	(.69,31.77)	(.68,22.37)
T3↓	5.72	8.47	.68	(.47,.96)	(.47,.96)
T4↑	.77	.39	1.98	(.48,11.55)	(.48,9.38)
T4↓	.10	.39	.25	(.005,3.08)	(1.13,2.64)
FTI↑	.29	0			
FTI↓	0	.26			
GLU	15.19	17.27	.88	(.71,1.09)	(.71,1.094)
TEST↑	.48	.52	.93	(.20,4.67)	(.22,4.098)
TEST↓	4.93	6.37	.77	(.52,1.16)	(.52,1.15)

Appendix XVIII (Cont)

MEAN SHIFTS FOR SELECTED CLINICAL END POINTS

CLINICAL PARAMETERS	MEAN VALUE RH	C	MEAN SHIFT
Conceptions per Participants	2.80	2.79	.0036
Mean Number of Marriages	1.24	1.22	.0164
Ulnar Nerve Cond (Above)	55.89	56.12	-0.004
Ulnar Nerve Cond (Below)	60.52	60.71	-0.003
Peroneal	48.23	48.93	-0.014
Fatigue Score (HS ed)	15.33	13.64	.1239
Anger Score (HS ed)	11.27	9.99	.1281
Erosion (HS ed)	22.34	20.00	.1170
Anxiety (HS ed)	24.62	21.91	.1237
Depression (HS ed)	5.79	5.30	.0925
Fatigue (Coll ed)	12.79	12.83	-.0031
Anger (Coll ed)	9.55	9.46	.0095
Erosion (Coll ed)	20.19	19.90	.0146
Anxiety (Coll ed)	21.23	20.51	.0351
Depression (Coll ed)	5.22	4.46	.1704
Cornell Index (HS ed)	9.21	6.44	.4301
Cornell Index (Coll ed)	3.66	3.44	.0640
MMPI Validity Scale (HS ed)	1.85	1.73	.0694
MMPI Defensiveness Scale (HS ed)	51.99	52.03	-.0008
MMPI Consistency (HS ed)	51.95	50.65	.0257
MMPI Denial (HS ed)	53.95	55.63	-.0302
MMPI Hypochondria (HS ed)	59.74	57.22	.0440
MMPI Depression (HS ed)	60.47	58.39	.0356
MMPI Hysteria (HS ed)	60.12	58.90	.0207
MMPI Psychopathic (HS ed)	56.38	55.89	.0088
MMPI Masc/Fem (HS ed)	55.94	54.85	.0199
MMPI Paranoia (HS ed)	51.72	50.68	.0205
MMPI Anxiety (HS ed)	57.27	55.59	.0302
MMPI Schizo (HS ed)	57.53	55.97	.0279
MMPI Mania (HS ed)	56.03	54.49	.0283
MMPI Social (HS ed)	52.31	50.80	.0297
MMPI Validity (Coll ed)	1.48	1.95	-.241
MMPI Defensiveness (Coll ed)	50.26	50.33	-.0014
MMPI Consistency (Coll ed)	48.74	48.44	.0062
MMPI Denial (Coll ed)	58.46	58.41	.0009
MMPI Hypochondria (Coll ed)	55.42	54.65	.0141
MMPI Depression (Coll ed)	55.34	54.57	.0141
MMPI Hysteria (Coll ed)	59.75	59.32	.0072
MMPI Psychopathic (Coll ed)	55.21	55.66	-.0081
MMPI Masc/Fem (Coll ed)	59.15	57.87	.0221
MMPI Paranoia (Coll ed)	53.62	53.26	.0068
MMPI Anxiety (Coll ed)	53.62	54.18	-.0103
MMPI Schizo (Coll ed)	54.70	54.89	-.0035
MMPI Mania (Coll ed)	55.22	54.05	.0216
MMPI Social Introversion (Coll ed)	46.83	47.50	-.0141
Verbal IQ (HS ed)	110.61	101.73	.0873
Verbal IQ (Coll ed)	117.00	116.84	.0014
Perf IQ (HS ed)	102.40	104.14	-.0167
Perf IQ (Coll ed)	113.70	112.37	.0118

Appendix XVIII (Cont)

MEAN SHIFTS FOR SELECTED CLINICAL END POINTS

CLINICAL PARAMETERS	MEAN VALUE RH	MEAN VALUE C	MEAN SHIFT
Full Scale IQ (HS ed)	101.18	102.74	-.0152
Full Scale IQ (Coll ed)	117.30	116.59	.0061
SGOT	33.0	33.1	-.0030
SGPT	20.3	20.5	-.0098
GGPT	40.1	39.3	.0204
Alk Phos	7.69	7.52	.0226
T Bili	.57	.58	-.0172
D Bili	.23	.24	-.0417
LDH	142.1	141.7	.0028
Chol	212.2	216.6	-.0203
Trig	121.9	124.1	-.0177
Uroporphyrins	30.2	30.8	-0.0195
Coproporphyrins	30.8	30.8	0.0
d-Aminolevulinic Acid	2337.1	2371.4	-0.0145

Appendix XIX

SPOUSE AND PARTICIPANT REPORTED BIRTH DEFECTS
NOT MEETING STUDY CRITERIA

ICD	NAME	Ranch Hand	Original Comparison	Total Comparison
140-239	Neoplasms Malignant melanoma-skin Uncertain behavior of skin Unspecified nature, ovarian	1	2	2
240-279	Endocrine-Metabolic-Nutritional-Immune Gout Cystic fibrosis Hypogammaglobulinemia Albinism(ocular)	4	1	3
280-289	Blood & Blood-Forming Chronic lymphadenitis	0	1	2
290-319	Mental Hyperkinetic syndrome Dyslexia Learning disability Mental retardation	8	2	8
320-389	Nervous System & Sense Organs Epilepsy Meningitis Unspecified brain damage Polyneuropathy Visual disturbance Lagophthalmos Esotropia Cerebral palsy Congenital deafness Endophthalmitis Amblyopia Acoustic nerve disorder Hearing loss Chronic otitis media	21	16	23
390-459	Heart Disease Unspecified	1	0	2
460-519	Respiratory Allergy Asthma Pulmonary congestion & hypostasis Unspecified disease of respiratory system	7	4	6
520-579	Digestive Tooth disorders Esophagitis Unspecified hernia Ruptured rectum	5	4	6
580-629	Genitourinary Kidney disorders	5	2	2
680-709	Skin and Subcutaneous Tissue Eczema Unspecified skin disorders	8	0	2

Appendix XIX (continued)

SPOUSE AND PARTICIPANT REPORTED BIRTH DEFECTS
NOT MEETING STUDY CRITERIA

ICD	NAME	Ranch Hand	Original Comparison	Total Comparison
710-739	Musculoskeletal & Connective Tissue	2	3	6
	Arthralgia			
	Juvenile osteochondrosis of spine			
	Scoliosis			
	Arthrogryposis			
	Foot Deformity			
760-779	Conditions Originating in the Perinatal Period	32	31	42
	Premature			
	Hyaline membrane disease			
	Birth trauma			
	Atelectasis			
	Perinatal infection			
	RH ISO immunization			
	Neonatal jaundice			
	Transient neonatal electrolyte disturbance			
	Unspecified hematological disorder			
	Complications of labor & delivery			
	ABO ISO Immunization			
	Fetal hemorrhage			
780-799	Symptoms, Signs, and Ill-Defined Conditions	26	15	18
	Sudden death syndrome			
	Functional & undiagnosed cardiac murmurs			
	Enlarged lymph glands			
	Others			
	Jaundice, not of newborn			
	Rash			
	Other umbilical hernia			
	Swelling or lump			
	Lack of physiological development			
	Biliuria			
TOTAL		120	81	122

Appendix XX

OBSERVED CANCER VERSUS SEER* DATA EXPECTED IN 1174
RANCH HANDERS (RH) AND 956 ORIGINAL COMPARISONS (COM)
(QUESTIONNAIRE COMPLIANT)

Group	Cancer Type	Expected	Observed	Probability of Observed	Probability of Observed or Larger
RH	Testicle	1.09656	2	.2009	.2997
RH	Bladder	1.05838	2	.1945	.2857
RH	Digestive	4.00809	0	.0180	1.0000**
RH	Lip and Oral	1.31739	4	.0336	.0448***
RH	Genitourinary	3.59195	6	.0822	.1545
COM	Testicle	.912751	0	.4012	1.0000
COM	Bladder	.927593	1	.3671	.6047
COM	Digestive	3.52238	4	.1898	.4684
COM	Lip and Oral	1.15221	2	.2099	.3201
COM	Genitourinary	3.11509	2	.2154	.8179

*Surveillance, Epidemiology, and End Results (SEER)
**Statistically significant deficit
***Statistically significant excess