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A. Young

EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDE ORANGE

EPIDEMIOLOGY DIVISION

USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)

BROOKS AFB, TEXAS

EXECUTIVE OVERVIEW
PROJECT RANCH HAND II

- OPERATIONAL BACKGROUND
- STUDY GOALS
- EPIDEMIOLOGIC STUDY DESIGN
- PRIMARY DATA COLLECTION METHODS
- STATISICAL METHODOLOGY
- SUMMARY

PROJECT RANCH HAND II

PURPOSE OF THE STUDY: TO DETERMINE WHETHER LONG TERM HEALTH EFFECTS EXIST AND CAN BE ATTRIBUTED TO OCCUPATIONAL EXPOSURE TO HERBICIDE ORANGE

EPIDEMIOLOGIC STUDY DESIGN

COMPONENTS OF THE PROBLEM

HAVE THERE BEEN, ARE THERE CURRENTLY, OR WILL THERE BE IN THE REASONABLY FORESEEABLE FUTURE , ANY ADVERSE HEALTH EFFECTS AMONG FORMER RANCH HAND PERSONNNEL CAUSED BY REPEATED OCCUPATIONAL EXPOSURE TO 2,4,5-T HERBICIDE AND ITS CONTAMINANT, TCDD (DIOXIN) ?

GOALS OF STUDY

PREMISE: GOALS ARE INTERDEPENDENT

1. ASSESS HEALTH EFFECTS ——————————— HEALTH

   INDENTIFY INDIVIDUALS WITH ADVERSE HEALTH EFFECTS (PHYSICAL AND PSYCHOLOGICAL) FROM TCDD EXPOSURE, AND IDENTIFY OTHERS AT INCREASED RISK

2. SATISFY SOCIAL CONCERN FROM LAY AND ——————— POLITICAL SCIENTIFIC COMMUNITIES

3. CLARIFY COMPENSATION ISSUE ——————————— LEGAL

OPERATING ASSUMPTION

OPERATION RANCH HAND PERSONNEL WERE PROBABLY EXPOSED TO 2,4,5-T AND TCDD TO A SIGNIFICANTLY GREATER DEGREE THAN US ARMY GROUND PERSONNEL

IMPLYING THAT RANCH HAND PERSONNEL WOULD DEVELOP MORE ACUTE/CHRONIC CLINICAL SYMPTOMS FROM THE EXPOSURES AND WOULD MANIFEST THEM SOONER THAN THE US ARMY PERSONNEL

AIR FORCE PROJECT RANCH HAND

EPIDEMIOLOGIC APPROACH

STUDY PHASE	METHODS
• MORTALITY STUDY	PERSON TRACKING, RECORD REVIEWS
• MORBIDITY STUDY	BASELINE QUESTIONNAIRE, PHYSICAL EXAM
• FOLLOW-UP STUDY	ADAPTIVE QUESTIONNAIRES, PHYSICAL EXAMS

THREE PHASE APPROACH REQUIRED

EPIDEMIOLOGIC STUDY DESIGN

CLASSIC APPROACH:

LITERATURE REVIEW → PILOT STUDY → RETROSPECTIVE → X-SECTIONAL → NONCONCURRENT PROSPECTIVE STUDY →

PROJECT RANCH HAND II:

LITERATURE REVIEW
- MORTALITY
  - MORBIDITY
    - FOLLOW-UP →

PROSPECTIVE →

RANCH HAND II

EPIDEMIOLOGIC STUDY DESIGN
GROUP SELECTION, RATIONALE

PRIMARY EXPOSED GROUP	CONTROL GROUP NOT EXPOSED TO H.O.
C-123 RANCH HAND; CREW+SUPPORT	⟷ C-130, CREW+SUPPORT

- •• STUDY REQUIREMENT
  - HIGH RELATIVE EXPOSURE TO HERBICIDE ORANGE (H.O.)
  - POPULATION IDENTIFIABLE
- NO JOB EXPOSURE TO H.O.
- LARGE N, TIGHT MATCHING FEASIBLE
- SIMILAR COMBAT STRESS AS C-123 CREWS
- LIFESTYLE AND PERSONALITY SIMILAR TO C-123 CREWS

•• ATTEMPT TOTAL ASCERTAINMENT OF BOTH GROUPS TO CONTROL HIDDEN MORTALITY EFFECTS

EPIDEMIOLOGIC STUDY DESIGN

- **ANCILLARY STUDY GROUPS**
  - DRUM HANDLERS
  - SECONDARY MAINTENANCE PERSONNEL
  - ARMY OBSERVERS
  - HELICOPTER CREWS
  - EXPERIMENTAL SPRAY UNITS
  - ALL OTHERS
- **FACTORS**
  - NUMERATOR: VOLUNTEER BIAS
  - DENOMINATOR: POPULATION AT RISK; UNKNOWN
  - CONTROL GROUP: MOOT
- **PLAN**
  - ALL DATA SUBSETTED, ANALYZED SEPARATELY
  - DATA AND INTERPRETATIONS, IF ANY, ANECDOTAL

RANCH HAND PERSONNEL

POTENTIAL FOR EXPOSURE

PILOTS, CO-PILOTS, NAVIGATORS	LOW
CREW CHIEFS, MAINTENANCE PERSONNEL	MODERATE
CONSOLE OPERATORS	HIGH

EXPOSURE INDEX CONSTRUCTION

SIMULANT STUDIES WITHIN AIRCRAFT (RICKENBACKER AFB OH)

- SKIN EXPOSURE 5:1 (CONSOLE OPERATOR VS PILOT)
- RESPIRATORY EXPOSURE

  PARTICLES 5:1 (CONSOLE OPERATOR VS PILOT)

  VAPOR 3:1 (CONSOLE OPERATOR VS PILOT)

RANCH HAND II

EPIDEMIOLOGIC STUDY DESIGN
SOME KNOWN/ESTIMATED POPULATION PARAMETERS

	EXPOSED GROUP (C-123)	CONTROL GROUP (C-130)
AGE RANGE:	28-62	25-65
SEX:	ALL MALE	ALL MALE
RACE:	OFFICER: ~100% WHITE ENLISTED: ~10-14% BLACK	~100% WHITE ~10-14% BLACK
CURRENT ACTIVE DUTY:	25% OFFICER: SENIOR MANAGEMENT ENLISTED: MIDDLE MANAGEMENT	20-25% SENIOR MANAGEMENT MIDDLE MANAGEMENT
PAST SERVICE EMPLOYMENT:	AEROSPACE INDUSTRY	AEROSPACE INDUSTRY
SOCIOECONOMIC: GENERAL LIFESTYLE:	SIMILAR TO CONTROL	SIMILAR TO STUDY

RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
RATIONALE FOR MATCHING PROCEDURE

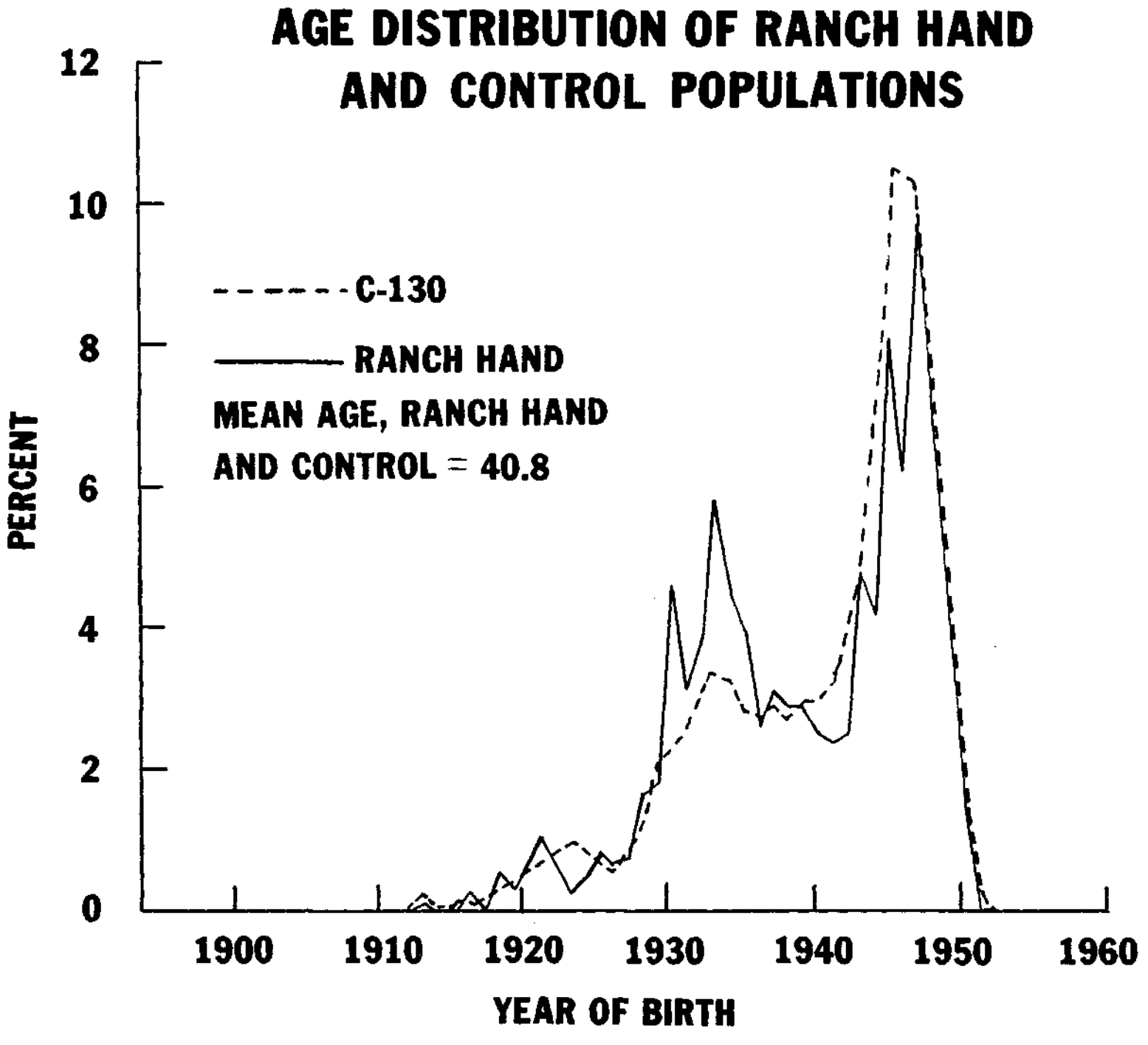
MATCHING PROCEDURE RATIONALE:

- EACH EXPOSED PERSON WILL HAVE A SET OF TEN CONTROLS, SELECTED ON BEST FIT BASIS
- ALLOWS STATISTICAL INTER-GROUP TESTS WITHOUT MAJOR ADJUSTMENTS
- PROVIDES BETTER FLEXIBILITY FOR MULTVARIATE TESTING

RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN

PRIORITIZED MATCHING VARIABLES: RATIONALE

- AGE, ±6 MONTHS: CONTROLS FOR ANY AGE-DEPENDENT EFFECTS
- AFSC: CONTROLS OFFICER-ENLISTED, RATED-NONRATED STATUS, ETC. (FIVE CATEGORIES) I.E., SOCIOECONOMIC MATCH
- LENGTH OF RVN TOUR ±6 MONTHS : CONTROLS COMBAT MORBIDITY/MORTALITY AND NEURO-PSYCH EFFECTS
- RACE, CAUCASIAN/ NON-CAUCASIAN: CONTROLS DISEASE RATES, CULTURAL BACKGROUND


AGE DISTRIBUTION OF RANCH HAND AND CONTROL POPULATIONS
12
10
8
6
4
2
0
PERCENT
C-130
RANCH HAND
MEAN AGE, RANCH HAND AND CONTROL = 40.8
1900
1910
1920
1930
1940
1950
1960
YEAR OF BIRTH

COMPUTER MATCHING

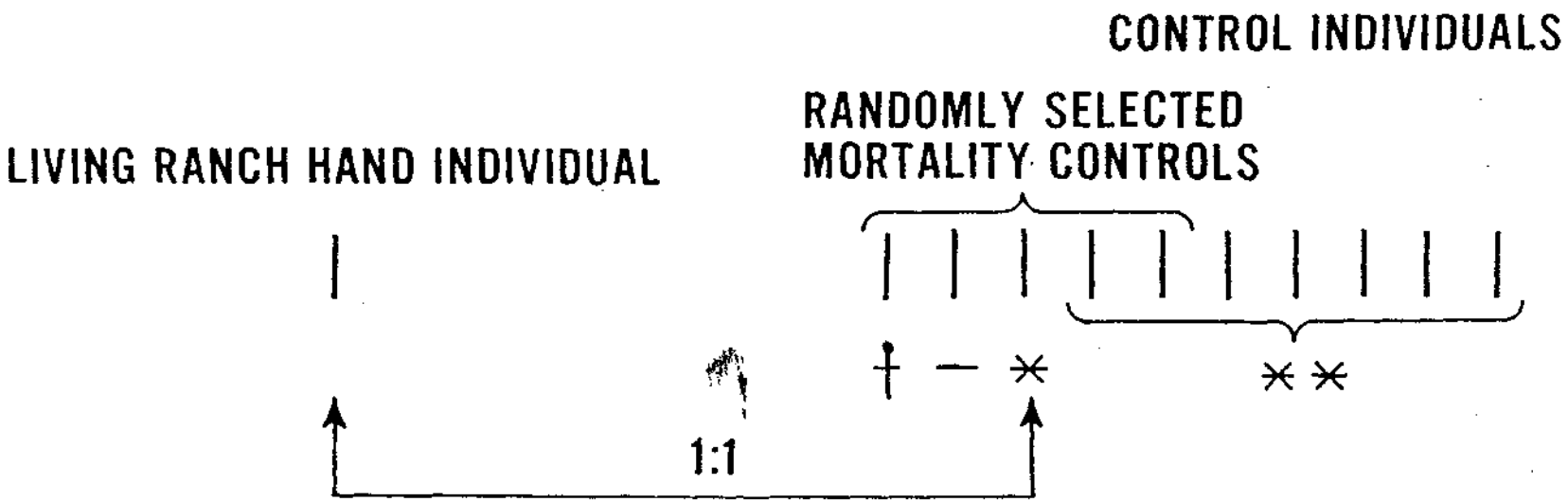
RANCH HAND TO CONTROL, 1:10

- 48% EXACT MATCH, BIRTH MONTH, JOB (5), TIME IN RVN, RACE, SEX
- 87% MATCH, ± ONE YEAR BIRTH, ALL OTHERS EXACT
- 95% + MATCH PREDICTED, ± 18 MONTHS BIRTH, ALL OTHERS EXACT

SELECTION OF THE CONTROL COHORT FOR THE MORTALITY ANALYSIS

EXPOSED GROUP	CONTROL COHORTS 1	2	3	4	5	6	7	8	9	10
R_1	$C_{1,1}$	$C_{1,2}$	$C_{1,3}$	$C_{1,4}$	$C_{1,5}$	$C_{1,6}$	$C_{1,7}$	$C_{1,8}$	$C_{1,9}$	$C_{1,10}$
R_2	$C_{2,1}$	$C_{2,2}$	$C_{2,3}$	$C_{2,4}$	$C_{2,5}$	$C_{2,6}$	$C_{2,7}$	$C_{2,8}$	$C_{2,9}$	$C_{2,10}$
R_3	$C_{3,1}$	$C_{3,2}$	$C_{3,3}$	$C_{3,4}$	$C_{3,5}$	$C_{3,6}$	$C_{3,7}$	$C_{3,8}$	$C_{3,9}$	$C_{3,10}$
•	•	•	•	•	•	•	•	•	•	
•	•	•	•	•	•	•	•	•	•	•
•	•	•	•	•	•	•	•	•	•	•
R_j	$C_{j,1}$	$C_{j,2}$	$C_{j,3}$	$C_{j,4}$	$C_{j,5}$	$C_{j,6}$	$C_{j,7}$	$R_{j,8}$	$C_{j,9}$	$C_{j,10}$

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



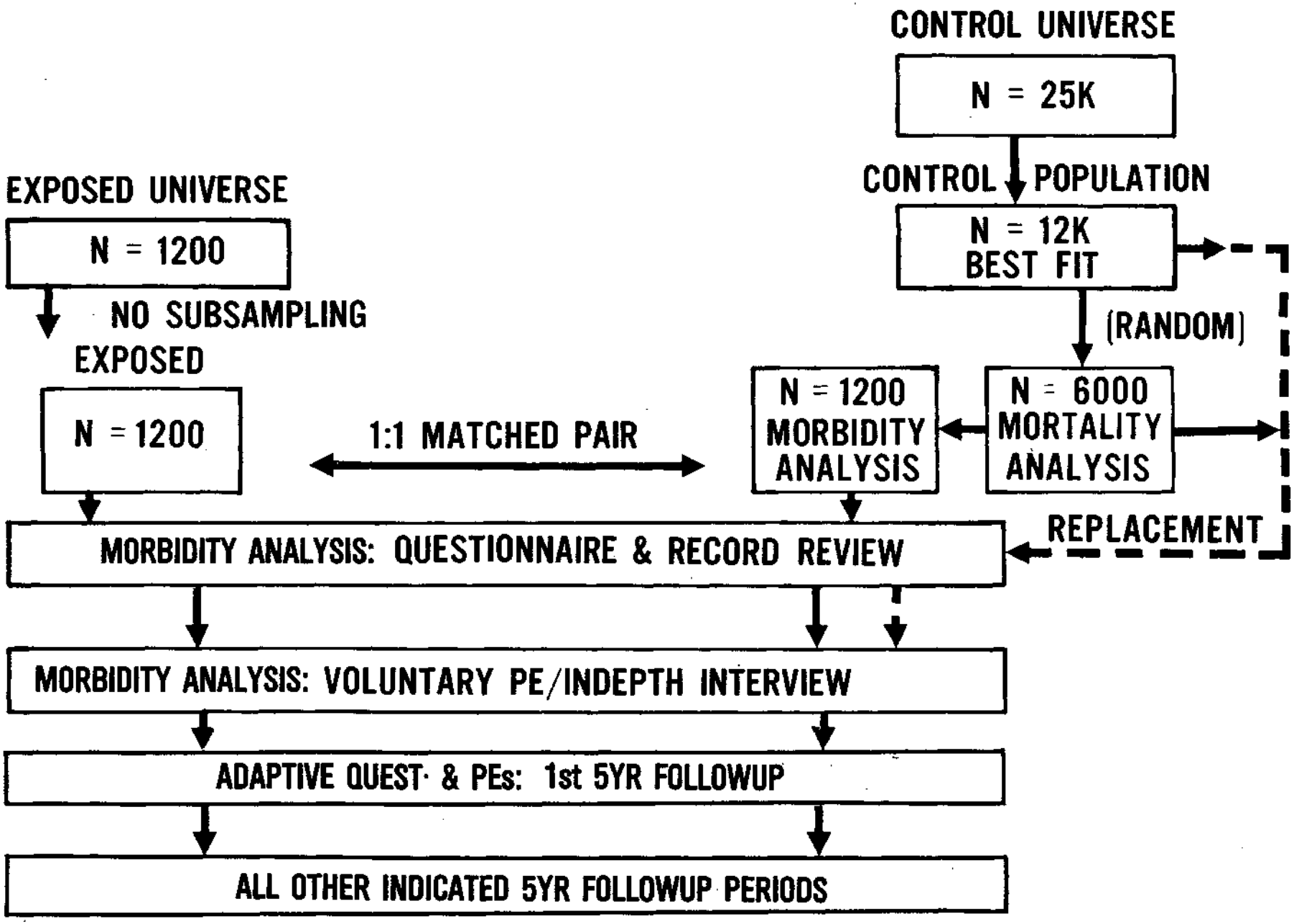
† DEAD

— UNWILLING

✳ VOLUNTEER

✳✳ REPLACEMENT CANDIDATES

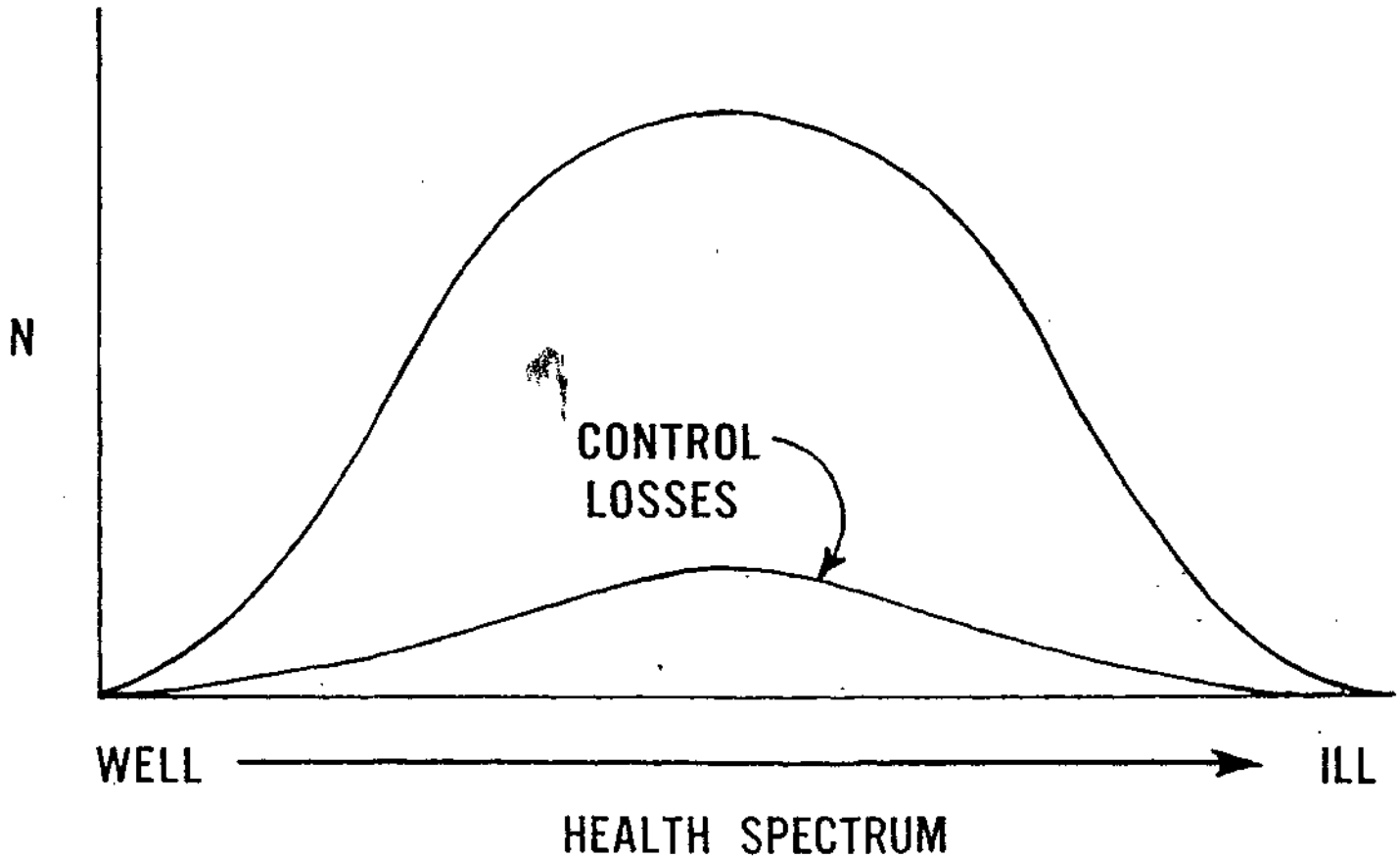
STUDY DESIGN SCHEMATIC



PURPOSE OF THE REPLACEMENT STRATEGY

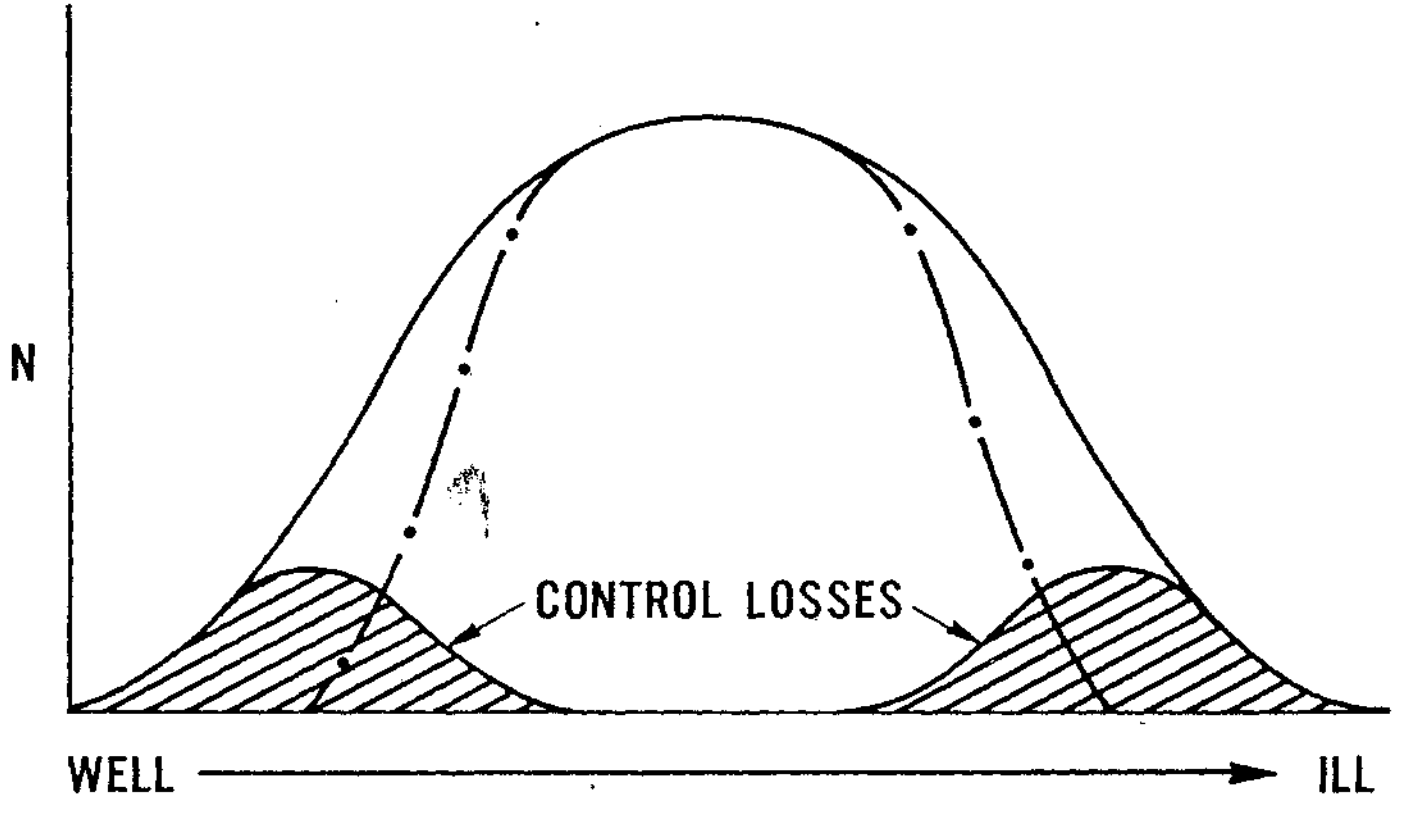
- CORRECT EXPECTED SELECTION BIAS
- ENHANCE STATISTICAL POWER

EFFECT OF RANDOM LOSS TO STUDY IN THE CONTROL POPULATION



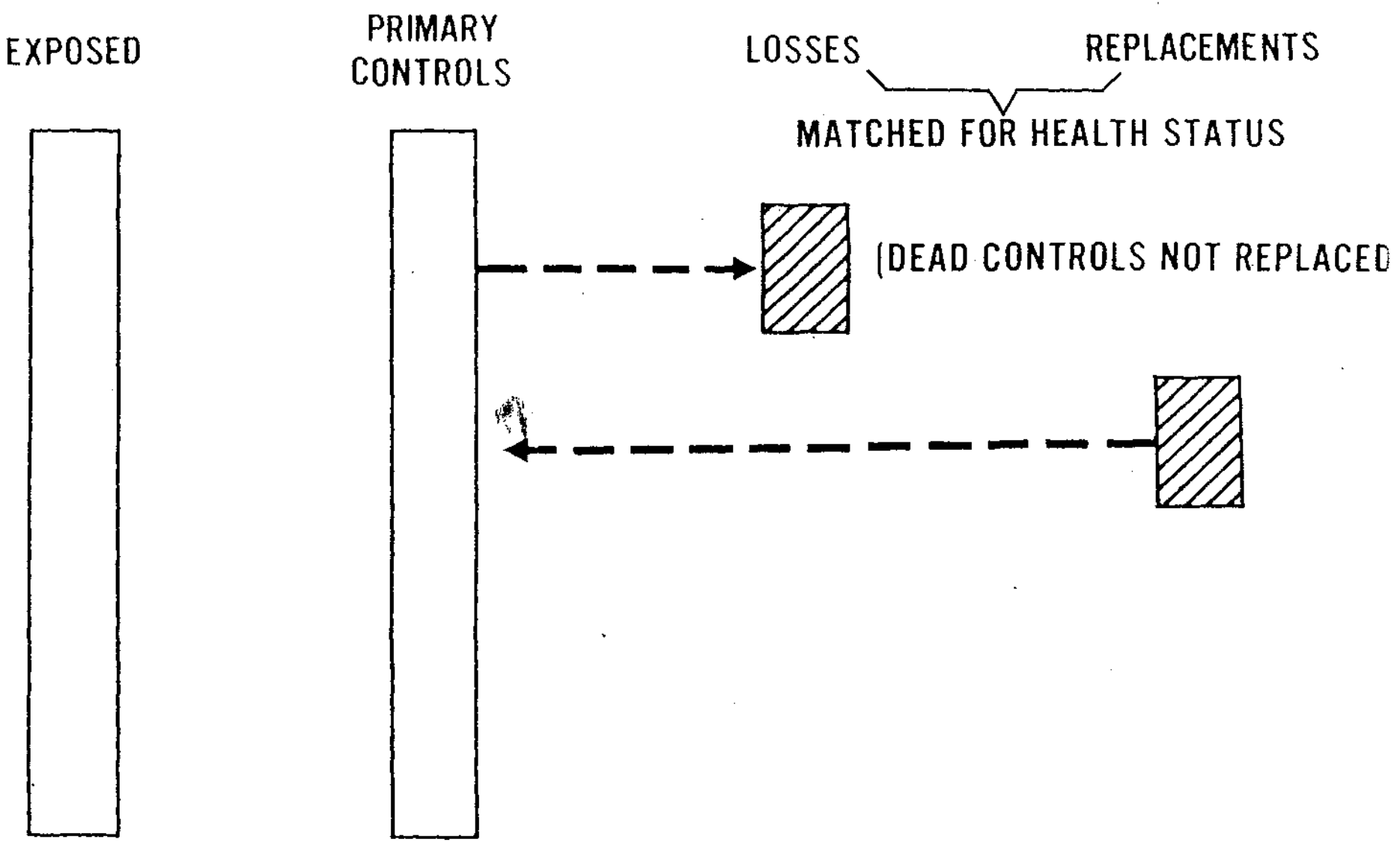
- NO ADVERSE EFFECT (BIAS) OTHER THAN LOSS OF STATISTICAL POWER FROM SMALL N.

EFFECT OF NON-RANDOM LOSS TO STUDY IN THE CONTROL POPULATION



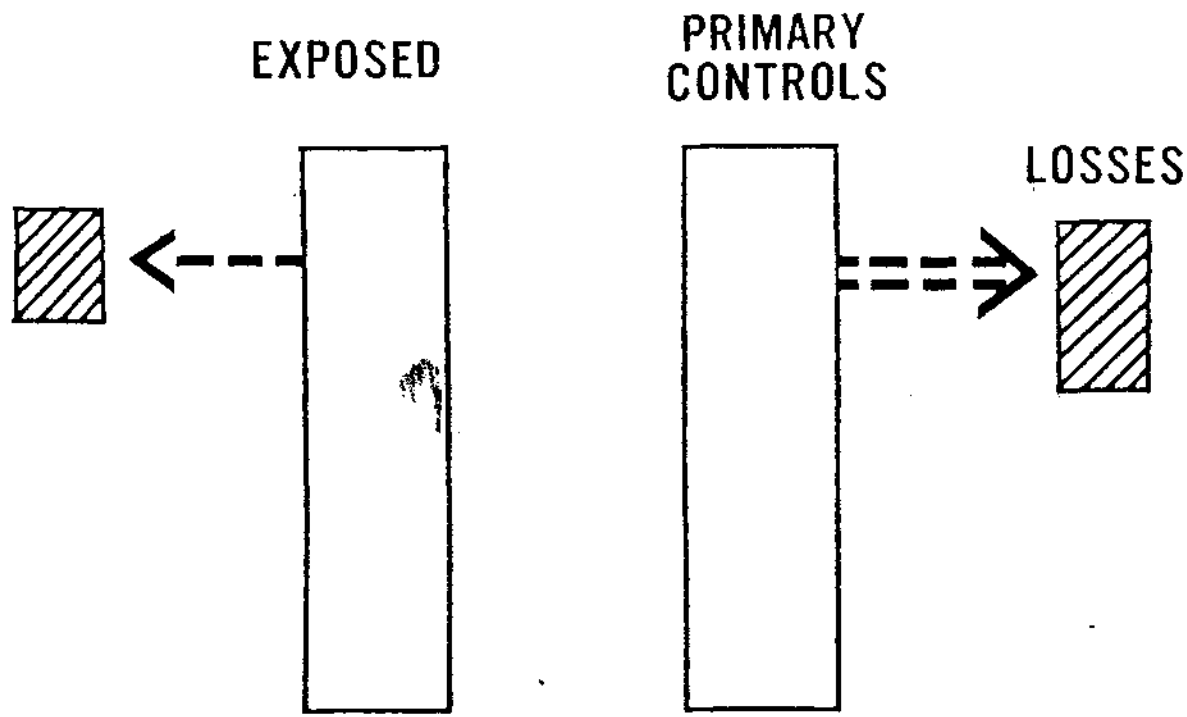
- IF CONTROL LOSSES ARE ILL, A SPURIOUS EFFECT IS ATTRIBUTED TO HERBICIDE EXPOSURE.
- IF CONTROL LOSSES ARE WELL, A TRUE/VALID HEALTH EFFECT IS DILUTED.

REPLACEMENT STRATEGY



RATIONALE OF REPLACEMENT

DILUTIONAL BIAS

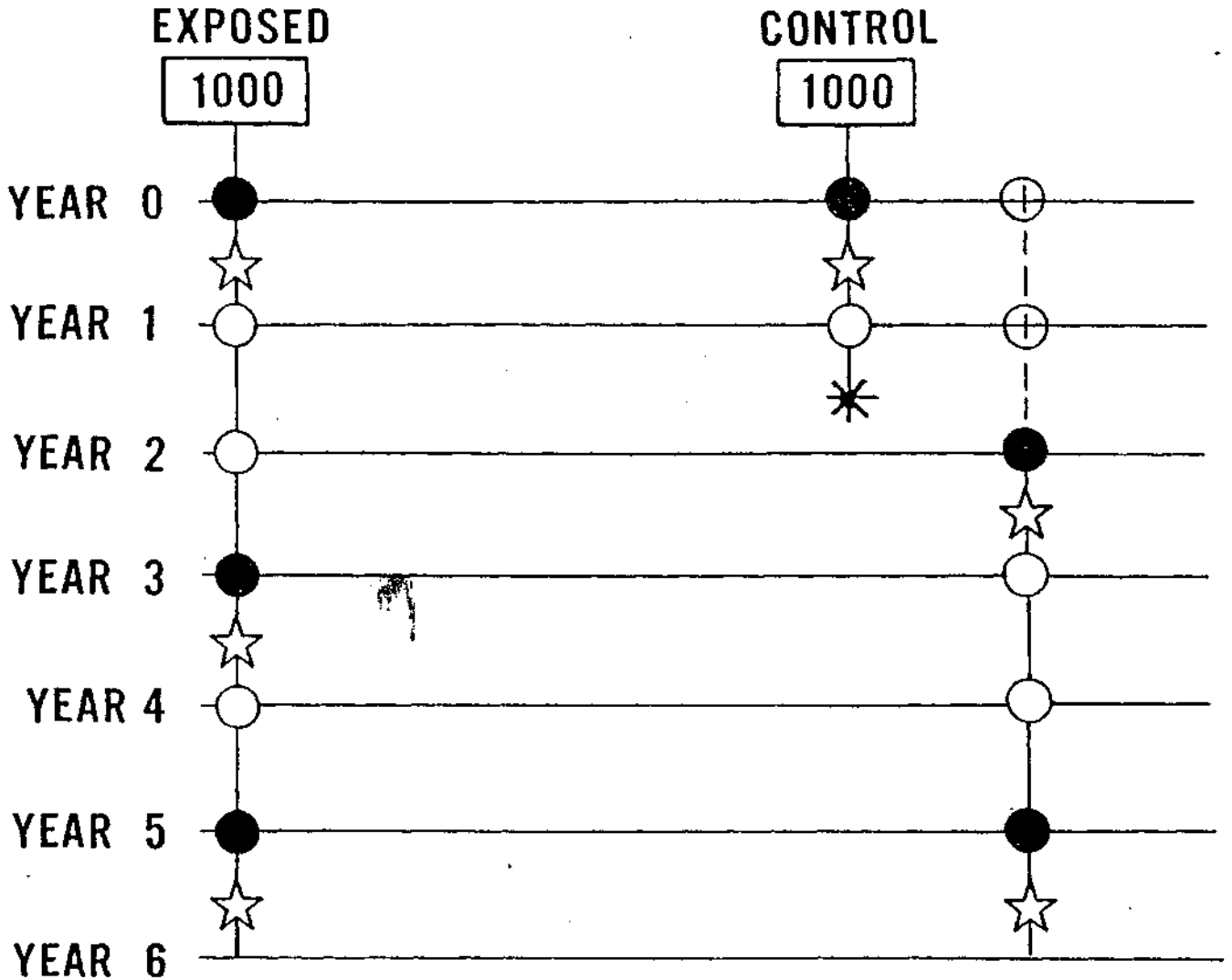


$P(L/W) > P(L/I)$ $P(L/W) >>> P(L/I)$

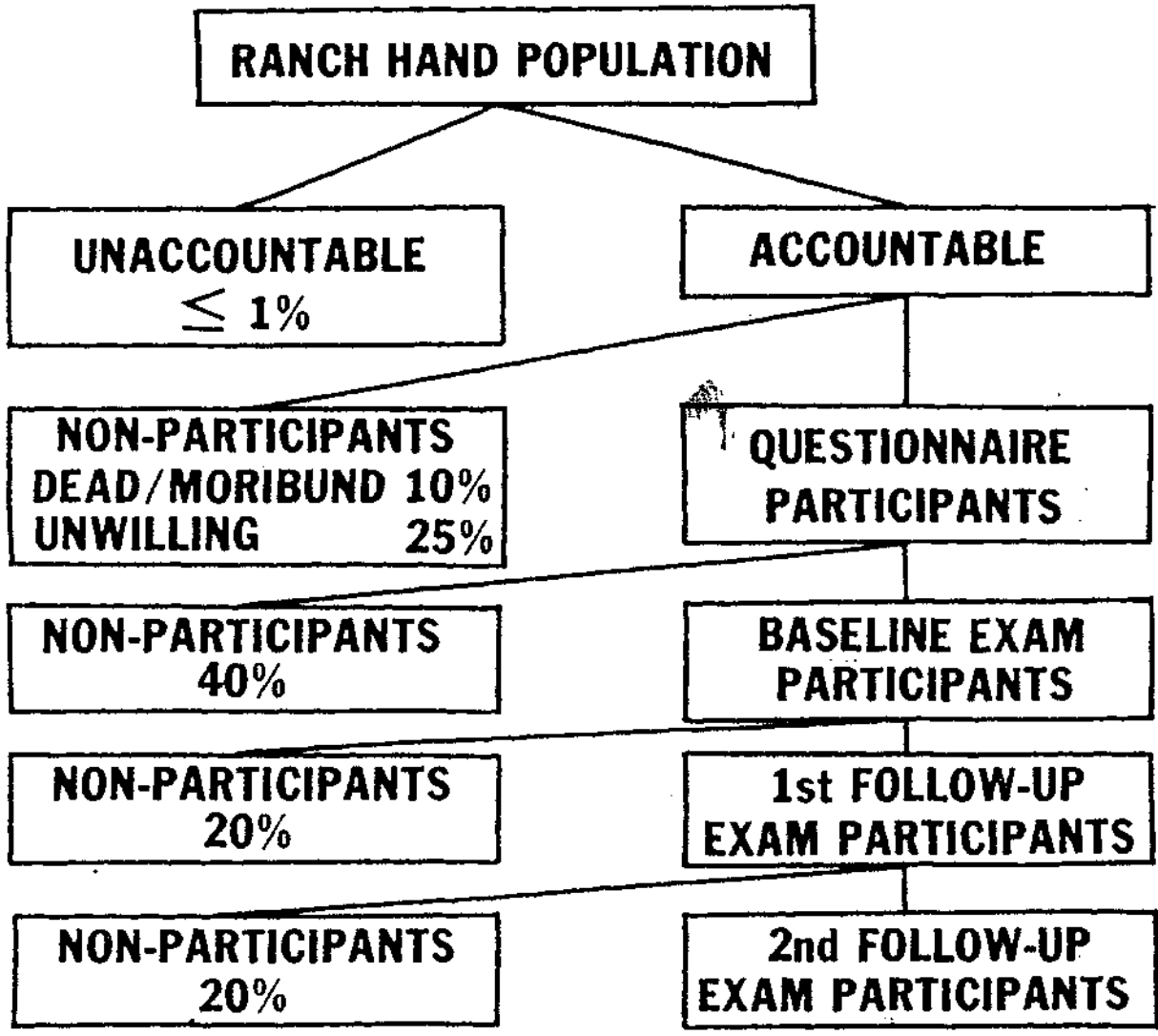
CONDITIONAL PROBABILITIES:

L = LOSS
W = WELL
I = ILL

CONTROL REPLACEMENT FOR THE MORBIDITY AND FOLLOW UP STUDIES



ESTIMATED IDENTIFICATION/PARTICIPATION OF THE RANCH HAND POPULATION



	RESPONSE ESTIMATE	ESTIMATED NUMBER OF PARTICIPANTS
RANCH HAND POPULATION	—	1200
ACCOUNTABLE	99%	1188
QUESTIONNAIRE PARTICIPANTS	65%	772
BASELINE EXAM PARTICIPANTS	60%	463
1st FOLLOW-UP EXAM PARTICIPANTS	80%	371
2nd FOLLOW-UP EXAM PARTICIPANTS	80%	297

RANCH HAND II
EPIDEMIOLOGIC STUDY DESIGN
FOLLOW-UP STUDY

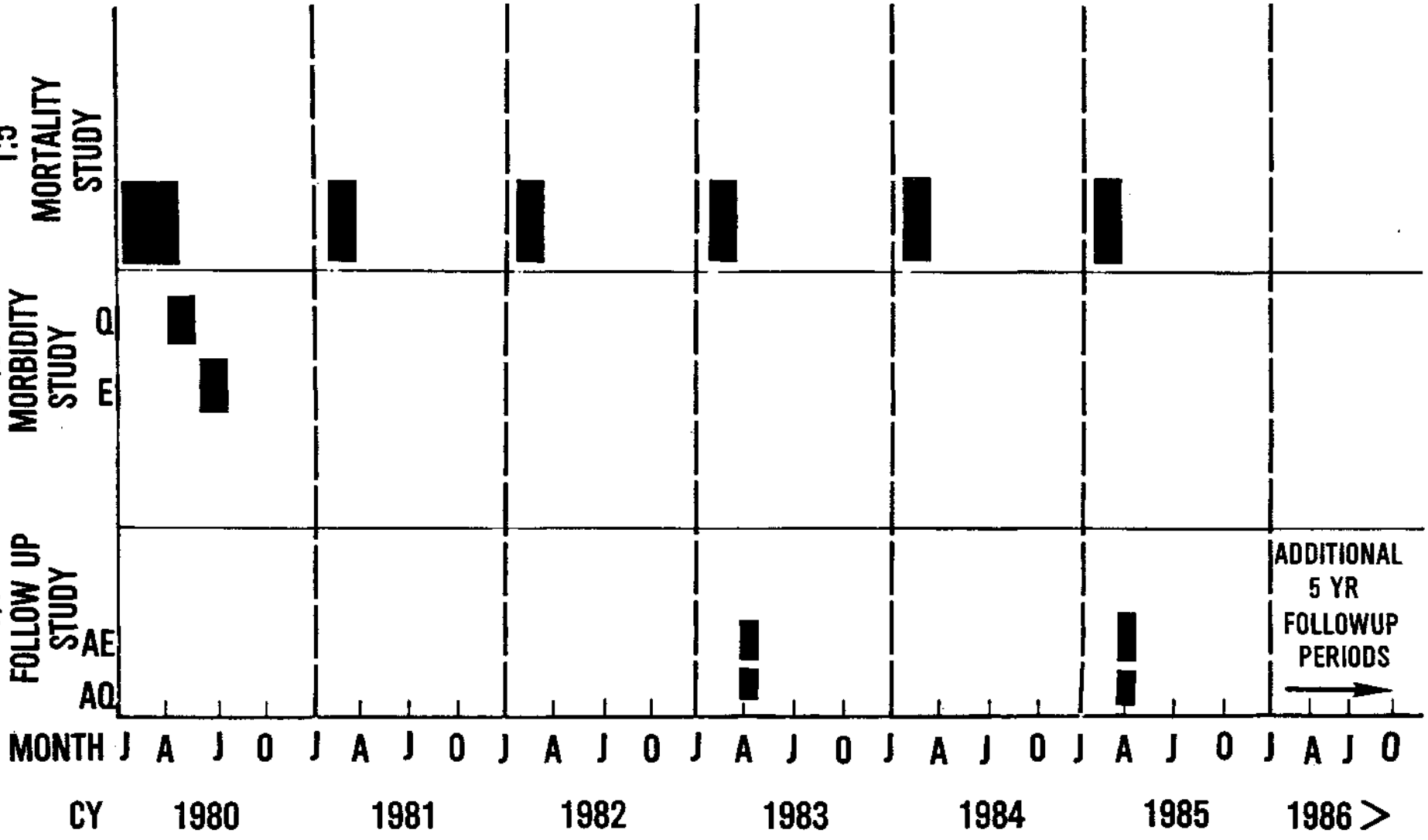
OVER 5 YEAR PERIOD; RENEWABLE 5 YEAR OPTIONS

"ADAPTIVE" QUESTIONNAIRE

"ADAPTIVE" PHYSICAL EXAMINATION

} IN YEARS 3 AND 5

PARTICIPATION SCHEMATIC FOR A GIVEN SUBJECT BY DATE AND STUDY PHASE



Q QUESTIONNAIRE
E PHYSICAL EXAMINATION
AE ADAPTIVE EXAMINATION
AQ ADAPTIVE QUESTIONNAIRE

INFORMATION SOURCES

- NATIONAL PERSONNEL RECORD CENTER, ST LOUIS
- AIR FORCE HUMAN RESOURCE LABORATORY
- MILITARY PERSONNEL RECORD CENTER
- AIR FORCE RESERVE/AIR NATIONAL GUARD
- UNIT HISTORIES AND PERSONAL REFERRALS

METHODS OF ASCERTAINMENT

NPRC

- MORNING REPORTS 1961-1966
- MILITARY PERSONNEL RECORDS
    - ALL VETERANS
        - UNITS OF ASSIGNMENT BY TIME/PLACE/STATUS
        - AIR FORCE SPECIALTY CODE (JOB) BY TIME
        - COMBAT FLYING HOURS
        - CUMULATIVE COMBAT MISSIONS
- MEDICAL RECORDS
    - INPATIENT/OUTPATIENT
        - VETERANS & DEPENDENTS
- PRESENT STATUS
    - RETIRED, RESERVES, DECEASED, VA CLAIM
    - ADDRESS AT TIME OF SEPARATION

DATA COLLECTION OVERVIEW

- MORTALITY DETERMINATION
- QUESTIONNAIRE
- RECORD REVIEWS
- PHYSICAL EXAMINATION

MORTALITY DETERMINATION

- MILITARY PERSONNEL RECORDS
- VETERANS ADMINISTRATION DEATH BENEFITS
- SOCIAL SECURITY ADMINISTRATION
- OTHER SOURCES: FAMILY, FRIENDS, SOCIAL ORGANIZATIONS, ETC.

QUESTIONNAIRE

PURPOSE

- COLLECT HEALTH DATA THAT CAN BE ANALYZED FOR HEALTH EFFECTS DUE TO HERBICIDE EXPOSURE
- CAPTURE DATA THAT WOULD BE LOST THROUGH LOW PHYSICAL EXAMINATION COMPLIANCE RATES

QUALITY

- DEVELOPMENT CONSULTATION CONTRACT
- INTERVIEWER QUALITY CONTROL
- PRETEST

VALIDITY

- QUESTIONS RESTRICTED
- VERIFIERS/BIAS INDICATORS
- CROSS REF TO MR, PE, AND INTERVIEW
- DEVELOPMENT OF QUESTION PHRASING

SECTIONS OF QUESTIONNAIRE

- DEMOGRAPHIC DATA
- MEDICAL PROBLEMS
  - IDENTIFICATION IN RELATION TO TIME
  - ICDA CODES
- PERSONAL HISTORY
- MARITAL HISTORY
- PROGENY
- OTHER EXPOSURES
  - OCCUPATION
  - HOBBIES
  - RESIDENCES
- VIETNAM EXPERIENCE HISTORY

RECORD REVIEW

- MEDICAL RECORDS (AF, VA, CIV)
- PERSONNEL RECORDS
- DEATH CERTIFICATES/AUTOPSY REPORTS
- BIRTH CERTIFICATES ON OFFSPRING

DATA REPOSITORY

- COMPUTER INTEGRATION OF:
  - ALL QUESTIONNAIRES (DIRECT ENTRY)
  - PSYCHOLOGICAL TESTING
  - PHYSICAL EXAMINATION
  - MEDICAL RECORDS
  - HISTORICAL AND NATIONAL PERSONNEL RECORD CENTER DATA
  - DEATH CERTIFICATES
  - BIRTH CERTIFICATES
- MASTER FILE ON EACH STUDY AND MATCHED CONTROL
- CONFIDENTIALITY WILL BE ASSURED
- RETRIEVAL
  - MOMENTARY RECALL
  - DATA ANALYSIS

POSSIBLE
DIAGNOSTIC INDICATORS
OF
HERBICIDE/DIOXIN TOXICITY

SOURCES OF INFORMATION

- ANIMAL STUDIES
- HUMAN CASE REPORTS
- EPIDEMIOLOGIC STUDIES
- VA CLAIMS / VA REPOSITORY
- VETERANS' CONCERNS

SUGGESTED ATTRIBUTABLE SYMPTOMS OF HERBICIDE/TCDD IN HUMANS

2,4-D	2,4,5-T (+TCDD)	TCDD
		• CHLORACNE
	• PORPHYRIA	• PORPHYRIA
	• HYPERPIGMENTATION	• HYPERPIGMENTATION
• ASTHENIA	• ASTHENIA	• ASTHENIA
• PERIPHERAL NEUROPATHY	• PERIPHERAL NEUROPATHY	• PERIPHERAL NEUROPATHY
• SWEATING/FEVER		
• CARDIAC DISTURBANCE	• CARDIAC DISTURBANCE	• CARDIAC DISTURBANCE
• RENAL DYSFUNCTION		
• LIVER DYSFUNCTION	• LIVER DYSFUNCTION	• LIVER DISFUNCTION
• GI DISTURBANCE	• GI DISTURBANCE	• GI DISTURBANCE
• HEADACHE		
• PNEUMONITIS		
		• HYPOTHYROIDISM
		• HEARING/SMELL DISTURBANCES
• CSF PROTEIN ABNORMALITIES		
• CONVULSIONS		

SUBJECTIVE SIGNS AND SYMPTOMS

ANXIETY

DEPRESSION

FATIGUE

APATHY

LOSS OF DRIVE

DECREASED LEARNING ABILITY

PARESTHESIAS

DECREASED LIBIDO

SLEEP DISTURBANCES

ANOREXIA

EPIDEMIOLGIC STUDIES

- HARDELL AND SANDSTROM (1978)

  CASE CONTROL STUDY OF SARCOMA PATIENTS

- TUNG (1973)

  INCREASES IN THE DIAGNOSIS OF PRIMARY LIVER CANCER

- ALSEA, OREGON (1979)

  SPONTANEOUS ABORTIONS IN SPRAYED AREAS OF OREGON

- AUSTRALIA AND NEW ZEALAND (1978)

  BIRTH DEFECTS IN SPRAYED AREAS

- SEVESO, ITALY (1976)

  HUMAN EFFECTS FOLLOWING AN INDUSTRIAL ACCIDENT

PRELIMINARY RESULTS OF THE SEVESO STUDIES

- ACUTE AND SUB- ACUTE EFFECTS:
  - CHLORACNE
  - IDIOPATHIC NEUROLOGICAL CONDITIONS
  - IDIOPATHIC HEPATOMEGALY
- NO EVIDENCE TO DATE OF :
  - IMMUNOLOGIC DISTURBANCES
  - CYOGENETIC ABNORMALITIES
  - FETOTOXICITY
  - TERATOGENICITY
  - CARCINOGENICITY

GENERAL EVALUATION

- PHYSICAL EXAMINATION
- URINALYSIS
- ELECTROCARDIOGRAM
- CHEST X-RAY
- VDRL/FTA

DERMATOLOGIC

- THOROUGH EXAMINATION FOR CHLORACNE: ACTIVE OR RESIDUAL LESIONS
- URINE PORPHYRINS AND PORPHOBILINOGEN
- SERUM STORED FOR SUBSEQUENT PORPHYRIN STUDIES AS TECHNOLOGY IMPROVEMENTS PERMIT
- PHOTOGRAPHS OF LESIONS
- DELTA ALA

HEPATIC/NEOPLASTIC

- PHYSICAL EXAMINATION
- CHOLESTEROL/HDL CHOLESTEROL
- TRIGLYCERIDES, SGOT, SGPT, GGTP, LDH

ANA AND HEPATITIS ANTIGENS AND ANTIBODIES
IF HEPATIC FUNCTION IS IMPAIRED

NEUROLOGICAL/PHYCHOLOGICAL

- THOROUGH NEUROLOGICAL EXAMINATION
- NERVE CONDUCTION VELOCITIES
- CPK
- PSYCHOLOGICAL BATTERY
  - MMPI
  - WAIS
  - WRAT
  - WECHSLER MEMORY SCALE I
  - CORNELL INDEX
  - HALSTEAD-REITAN

IMMUNOLOGIC/HEMOPOIETIC

- CBC
- SEDIMENTATION RATE
- PLATELET COUNT
- RBC INDICES
- SERUM ELECTROPHORESIS

IMMUNOELECTROPHORESIS, SKIN TESTING, AND QUANTITATIVE IMMUNOGLOBULIN DETERMINATIONS IF INDICATE BY HISTORY

ENDOCRINE/REPRODUCTIVE

- PHYSICAL EXAMINATION
- SEMEN ANALYSIS: NUMBER, MOTILITY, MORPHOLOGY
- LH, FSH, TESTOSTERONE
- FASTING AND 2 HOUR POST PRANDIAL SERUM GLUCOSE
- DIFFERENTIAL CORTISOL
- THYROID PROFILE (RIA)
- COMPLETE REPRODUCTIVE HISTORY

KARYOTYPING IF INDICATED BY HISTORY

ENHANCEMENT OF DATA QUALITY

- SINGLE CENTER
- BLIND ASSESSMENT
- FULLY QUALIFIED PERSONNEL
- COMPLIANCE WITH EXAMINATION PROTCOL
- ON-SITE MONITOR
- STRICT LABORATORY QUALITY CONTROL

PROJECT RANCH HAND II

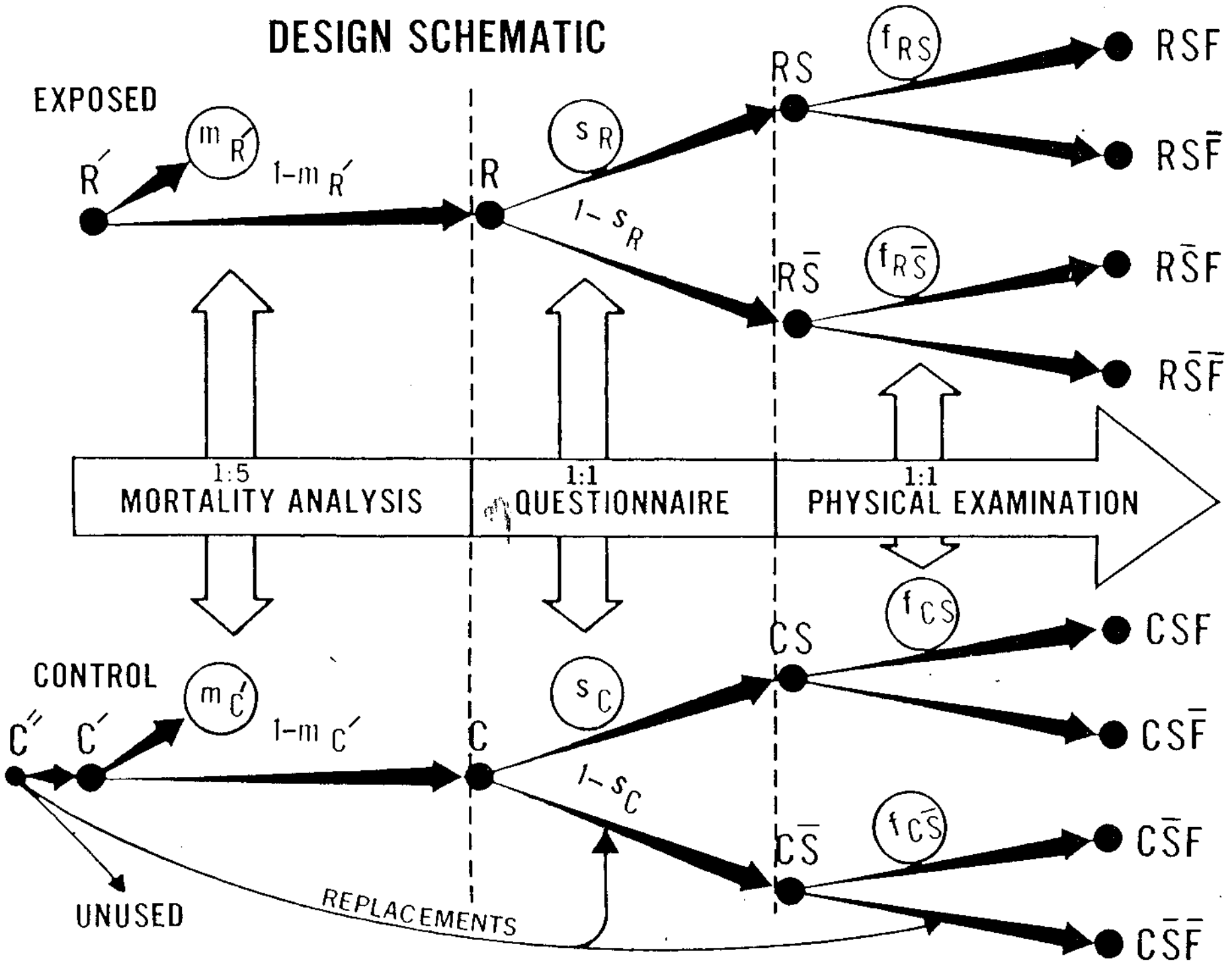
STATISTICAL METHODOLOGY

STATISTICAL METHODOLOGY - THRUSTS/GOALS

1. FULLY DEFINE STUDY POWER AND OPTIMIZE

2. ANALYZE BIAS SOURCES

3. INTERPRETATION


DESIGN SCHEMATIC
EXPOSED
R′
$m_{R'}$
$1-m_{R'}$
R
s_R
$1-s_R$
RS
f_{RS}
RSF
RS̄F̄
RS̄
$f_{RS̄}$
RS̄F
RS̄F̄
1:5
MORTALITY ANALYSIS
1:1
QUESTIONNAIRE
1:1
PHYSICAL EXAMINATION
CONTROL
C″
C′
$m_{C'}$
$1-m_{C'}$
C
s_C
$1-s_C$
CS
f_{CS}
CSF
CS̄F
CS̄
$f_{CS̄}$
CS̄F
CS̄F̄
UNUSED
REPLACEMENTS

INTERPRETATION OF HORIZONTAL COMPARISONS

OVERT EFFECT	SUBCLINICAL	OVER-REPORTING
$M_R \succ M_C$	$M_R = M_C$	$M_R = M_C$
$S_R \succ S_C$	$S_R = S_C$	$S_R \succ S_C$
$F_R \succ F_C$	$F_R \succ F_C$	$F_R = F_C$
$F_{RS} \succ F_{CS}$	$F_{RS} \succ F_{CS}$	$F_{RS} \prec F_{CS}$
$F_{R\bar{S}} \succ F_{C\bar{S}}$	$F_{R\bar{S}} \succeq F_{C\bar{S}}$	$F_{R\bar{S}} = F_{C\bar{S}}$
MORTALITY/SYMPTOM/ SIGN REGRESSION ON EXPOSURE	**SIGN REGRESSION ON EXPOSURE**	**NO REGRESSION ON EXPOSURE SEEN**

$$F_R = F_{RS}\, S_R + F_{R\bar{S}}\, (1 - S_R)$$

INDIVIDUAL EXPOSURE INDEX (E_j)

$$E_j = t_j \sum_i \left(f_{ij} \; c_{ij} \; p_{ij} \right) + h_j$$

FOR THE $i^{\underline{th}}$ MISSION:

f_{ij} = FRACTION 2,4,5 -T SPRAYED

c_{ij} = DIOXIN CONCENTRATION

p_{ij} = CREW POSITION

t_j = AVERAGE MISSION DURATION

h_j = SPECIFIC EXPOSURE HISTORY

MORTALITY ASSESSMENT

- THREE CATEGORIES: ALIVE, DEAD, UNACCOUNTED
- WILL MAINTAIN UNACCOUNTED $<$ 1%

METHODS FOR MORTALITY ANALYSIS

1. ESTIMATE STANDARDIZED MORTALITY RATIO (SMR) USING ARMITAGE APPROACH.

2. ESTIMATE SMR USING BRESLOW AND DAY MULTIPLICATIVE MODEL.

3. LOGISTIC MODELS (WALKER AND DUNCAN).

4. SURVIVAL MODELS (COX).

5. NONPARAMETRIC MATCHED PAIR SURVIVAL ANALYSIS (WEI).

(ARMITAGE, 1971)

	RANCH HAND			CONTROLS		
AGE GROUP	PERSON YEARS	DEATHS	DEATH RATE	PERSON YEARS	DEATHS	DEATH RATE
1	P_{11}	m_{11}	r_{11}	P_{21}	m_{21}	r_{21}
2	P_{12}	m_{12}	r_{12}	P_{22}	m_{22}	r_{22}
3	P_{13}	m_{13}	r_{13}	P_{23}	m_{23}	r_{23}
⋮	⋮	⋮	⋮	⋮	⋮	⋮
k	P_1k	m_1k	r_1k	P_2k	m_2k	r_2k

$$M = \frac{\sum_{j=1}^{k} mij}{\sum_{j=1}^{k} Pijr_2j}$$

$$SMR = M \times 100$$

(BRESLOW AND DAY, 1975)

- $\lambda_{ijk} = \theta_i \phi_j \psi_k$
- MAXIMUM LIKELIHOOD

LOGISTIC MODEL

$$p = \frac{e^{Z}}{1 + e^{Z}}$$

$$Z = \alpha + \beta_1 A + \beta_2 T + \beta_3 R + \beta_4 E + \beta_5 AE + \ldots$$

A= AGE

T = TOUR LENGTH

R = RACE INDICATOR

E = EXPOSURE INDEX

CONTROLS

RANCH HAND PERSONNEL	DEAD	ALIVE	TOTAL
DEAD	a	b	a+b
ALIVE	c	d	c+d
TOTAL	a+c	b+d	n

$$X^2 = \frac{|b-c|^2}{b+c}$$

COX SURVIVAL MODELS

$$\lambda = \lambda_0 e^{\underset{\sim}{\beta} \cdot \underset{\sim}{x}}$$

WEI MORTALITY METHOD

AGE AT EVENT (* = NO EVENT)			
EXPOSED PERSONNEL	MATCHED CONTROL	GEHAN/WEI SCORE	SIGN TEST
56	62	-4	-1
59	60 *	0	-1
53	58	-4	-1
57 *	55	1	+1
		-7 = Wn	-3

- Wn HAS KNOWN DISTRIBUTION FOR LARGE n
- TEST MORE POWERFUL THAN SIGN TEST

QUESTIONNAIRE DATA

- FOUR DATA TYPES: DICHOTOMOUS, POLYTOMOUS, COUNT, CONTINUOUS
- FOR CATEGORICAL RESPONSES USE LOG-LINEAR MODELS
- FOR ORDERED CATEGORICAL RESPONSES USE REGRESSION MODELS OF McCULLAGH
- FOR CONTINUOUS RESPONSES USE GENERALIZED LINEAR MODELS

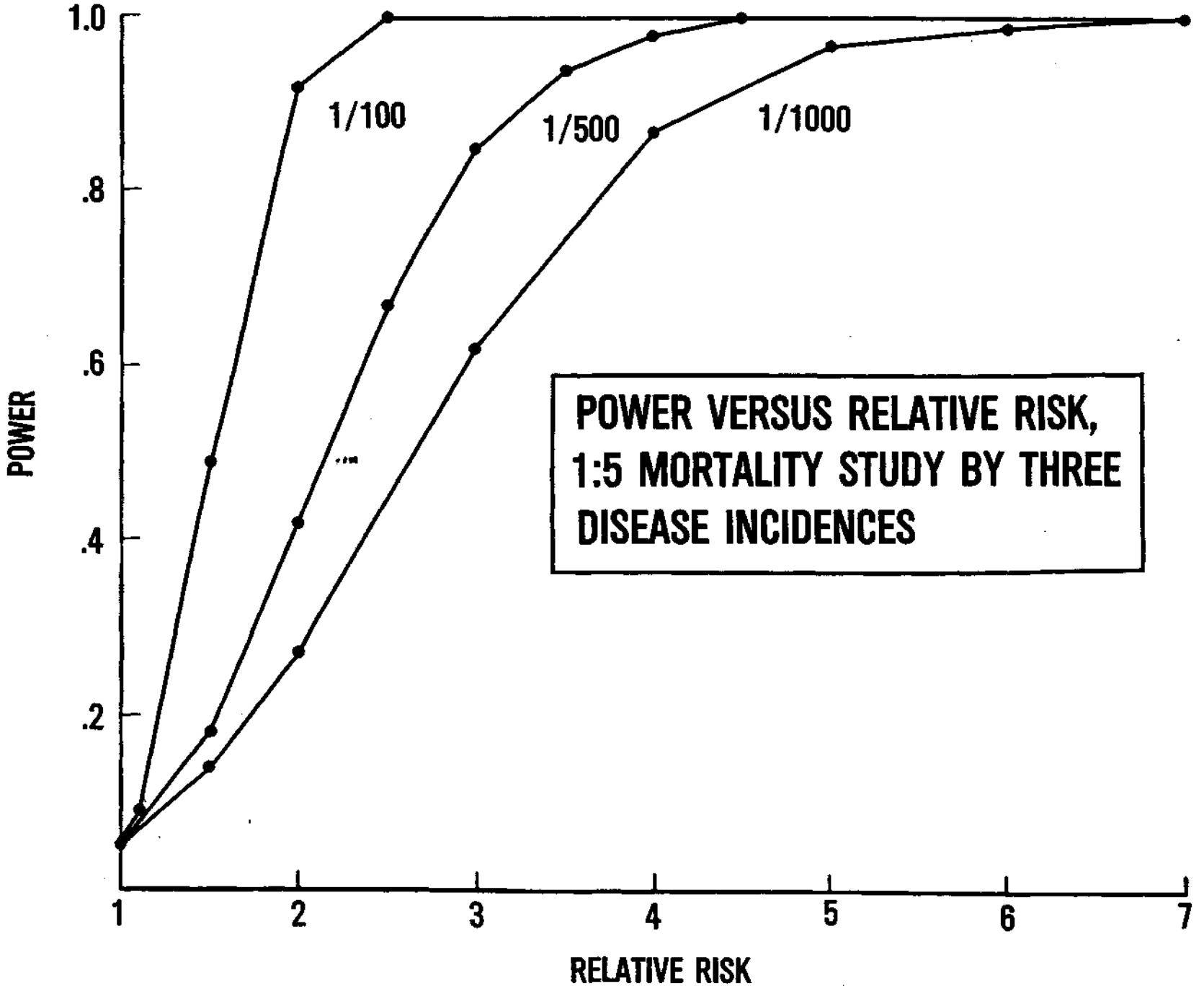
AGE CATEGORY / DISEASE CATEGORY	RANCH HAND PERSONNEL				CONTROLS			
	1	2	3	4	1	2	3	4
1	x_{111}	x_{112}	x_{113}	x_{114}	x_{211}	x_{212}	x_{213}	x_{214}
2	x_{121}	x_{122}	x_{123}	x_{124}	x_{221}	x_{222}	x_{223}	x_{224}
3	x_{131}	x_{132}	x_{133}	x_{134}	x_{231}	x_{232}	x_{233}	x_{234}
4	x_{141}	x_{142}	x_{143}	x_{144}	x_{241}	x_{242}	x_{243}	x_{244}

$$\ln m_{ijk} = u + u_1(i) + u_2(j) + u_3(k) + u_{12}(ij) + u_{13}(ik) + u_{23}(jk) + u_{123}(ijk)$$

RANCH HAND CATEGORY \ CONTROL CATEGORY	1	2	3	4
1	n_{11}	n_{12}	n_{13}	n_{14}
2	n_{21}	n_{22}	n_{23}	n_{24}
3	n_{31}	n_{32}	n_{33}	n_{34}
4	n_{41}	n_{42}	n_{43}	n_{44}

PHYSICAL EXAMINATION DATA

- SAME DATA TYPES AS QUESTIONNAIRE
- TO VALIDATE QUESTIONNAIRE DATA
- TO ESTIMATE RATE OF OCCURENCE OF PHYSICAL FINDINGS
- TO EVALUATE RELATIONSHIP OF SYMPTOMS AND PHYSICAL FINDINGS
- ESSENTIALLY USE THE SAME STATISTICAL TESTS AS USED WITH QUESTIONNAIRE


1.0
.8
.6
.4
.2
POWER
1/100
1/500
1/1000
POWER VERSUS RELATIVE RISK, 1:5 MORTALITY STUDY BY THREE DISEASE INCIDENCES
1
2
3
4
5
6
7
RELATIVE RISK

MORBIDITY STUDY

POWER – DICHOTOMOUS VARIABLES

				POWER 1 - β			
P_1	P_2	REL RISK	r	n = 250	n = 350	n = 450	
.05	.01	5	0	.77	.82	.92	α = 0.05
.04	.01	4	0	.61	.75	.85	
.03	.01	3	0	.40	.51	.59	
.10	.05	2	0	.61	.75	.85	
.20	.10	2	0	.87	.94	.97	
.05	.01	5	.1	.89/.029	.94/.032	.98/.064	α = AS INDICATED
.04	.01	4	.1	.72/.033	.87/.038	.88/.041	
.03	.01	3	.1	.38/.020	.68/.046	.71/.077	
.10	.05	2	.1	.76/.055	.85/.048	.88/.048	
.20	.10	2	.1	.94/.043	.98/.046	.99/.057	

MORBIDITY STUDY
POWER-CONTINOUS VARIABLES

$\alpha = 0.05$, $\sigma_C/\mu_C = 0.1$, $\gamma = \mu_{RH}/\mu_C$

R	γ	POWER = $1-\beta$ n=180	POWER = $1-\beta$ n=450
.20	1.01	.20	.38
.20	1.02	.55	.88
.20	1.05	> .995	> .995
.70	1.01	.86	> .995
.70	1.02	> .995	> .995
.70	1.05	> .995	> .995

MORTALITY-MORBIDITY STUDIES
POWER STUDY-CARDIOVASCULAR DISEASE SETTING

NUMBER OF PAIRS	$\gamma = \beta$		$\gamma = .8\beta$	
	POWER NEGLECTING PAIRING	POWER WITH PAIRING	POWER NEGLECTING PAIRING	POWER WITH PAIRING
250	> .99	> .995	.93	.95
300	> .99	> .995	.96	.97
350	> .99	> .995	.97	.98

$\alpha = 0.05$

REPLACEMENT CONCEPT

- DERIVED FROM LIFE-TABLE METHODS EMPLOYING PERSON-YEAR DENOMINATORS FOR INCIDENCE COMPUTATIONS

  MATANOSKI ET. AL., AMER. J. EPID., 101, 1975
  SHEPS, MILBANK MEM. FUND., 44, 1966
  ELVEBACK, JASA, 53, 1958

- ADDRESSES BIAS AND POWER CONCERNS

$$P(X) = \alpha P_c(X) + \beta P_{nc}(X)$$

$$M = \alpha Mc + \beta Mnc$$

$$BIAS = Mc - M$$

REPLACEMENT CONCEPT : STEPS

1. USE ALL DATA AVAILABLE ON NONCOMPLIANT INDIVIDUALS
2. DEVELOP DISCRIMINANT FUNCTION FROM THIS DATA

$$D = (H_1, H_2, H_3; L_1, L_2)$$

"HEALTH FACTORS"	"LOGISTIC FACTORS"
H_1=SUBJECTIVE HEALTH ASSESSMENT	L_1=TIME FROM HOME
H_2=CURRENT USE OF LONG-TERM HEALTH CARE	L_2=TIME FROM WORK
H_3=ABSENTEEISM	

3. THE REPLACEMENT WILL HAVE SAME HEALTH PERCEPTION (H_1) AS THOSE LOST TO STUDY
4. OTHER FACTORS (H_2, H_3, L_1, L_2) WILL BE ASSESSED AFTER ENTRY INTO STUDY

STUDY DESIGN CONSIDERATIONS

- LACK OF MULTIPLE CLINICAL MARKERS OR RECOGNIZED END POINTS
- STUDY BIASES (+ AND -)
- MULTIPLE HERBICIDE ENVIRONMENT; CONFOUNDING VARIABLES
- HERBICIDE ORANGE EXPOSURE NOT QUANTIFIED
- RESPONSE RATES TO QUESTIONNAIRES AND PEs
- PEs MAY DETECT DISQUALIFYING DEFECTS
- VARIABILITY OF DATA

AIR FORCE RANCH HAND STUDY

ACHIEVEMENTS TO DATE

- COMPREHENSIVE LITERATURE REVIEW (2,500)
- CONTACT ESTABLISHED: ALL LEADING H.O. EXPERTS (5 VISITS)
- ENDORSEMENT BY RANCH HAND ASSOCIATION
- 15 M RECORDS BY COMPUTER; 37 K RECORDS, HAND SORT
- RANCH HAND GROUP FULLY IDENTIFIED
- BASIC SCIENTIFIC PROTOCOL SET
- BASIC STATISTICAL FORMATS AND DATA REPOSITORY SET

UNIQUE FEATURES OF THE PHYSICAL EXAMINATION

- COMPREHENSIVE BY NECESSITY
  - LITERATURE REVIEW
  - VETERANS CLAIMS/CONCERNS
- ESSENTIALLY A STANDARD EXAMINATION WITH EXPANDED EVALUATION OF:
  - BIOCHEMICAL FUNCTION
  - NEUROLOGICAL AND PSYCHOLOGICAL STATUS
- DATA COLLECTED FOR SCIENTIFIC AS WELL AS CLINICAL CONSIDERATIONS
  - ASSESSMENT WITHOUT KNOWLEDGE OF EXPOSURE STATUS
  - STRICT ADHERENCE TO EXAMINATION PROTOCOL
  - HISTORY NOT TAKEN BY THE EXAMINER
  - DATA NOT ANALYZED BY THE EXAMINER

COMPONENTS OF THE MEDICAL EVALUATION

- COMPREHENSIVE MEDICAL/SOCIAL/OCCUPATIONAL HISTORY INCLUDING A FERTILITY HISTORY OF THE SUBJECT AND HIS SPOUSE (S)

- COMPREHENSIVE PHYSICAL AND LABORATORY EVALUATION WITH EMPHASIS ON THE TARGET SYSTEMS/CONDITIONS