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Protocol
Univ. of California
Epidemiology Study
April 1982
Book I of I

CASE ID:_____

DATE:_____

TIME:_____START _____END

INTERVIEWER:_____

VETERANS INTERVIEW

VETERAN

QUESTIONNAIRE FOR AGENT ORANGE

DATE OF INTERVIEW:_____

INTERVIEWER ID#:_____

PLACE OF EXAMINATION:_____

First, I would like to ask you a few general questions about you and your family. This information is important for statistical purposes, to see how people in this survey compare with the rest of the population.

1. What is your full name?

NAME:_____
FIRST MIDDLE LAST

2. What is your birthdate?

RECORD:_____
MONTH DAY YEAR

3. Where were you born?

RECORD:_____
CITY STATE

4. What was the highest grade in school you completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL: SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

5. With which of the following racial or ethnic backgrounds do you identify? Would you say:

Black,..... 1
Hispanic,..... 2
Asian, or..... 3
White?..... 4
OTHER..... 5
→ SPECIFY:_____

6. What language was spoken in your home when you were growing up (up to age 16)?

ENGLISH.....01
SPANISH.....02
GERMAN.....03
JAPANESE.....04
CHINESE.....05
OTHER.....96
→ SPECIFY:_____

7. What is your present marital status? Are you:

Married,..... 1
Divorced,..... 2
Separated,..... 3
Widowed, or..... 4
Have you never been married?..... 5

8. In what month and year did you first enter the Armed Services?

RECORD:_____/_____
MONTH YEAR

9. What is your social security number?

RECORD: ___ ___ ___/___ ___/___ ___ ___ ___

10. Please tell me the different cities you lived in for at least 2 months, starting with the place you were born.

PLACES RESIDED (CITY, STATE)	DATES OF RESIDENCE FROM	TO
1.		
2.		
3.		
4.		
5.		
6.		

11. Who was the head of the household when you were growing up?

RECORD HEAD: _____

12. What was his/her major occupation during most of your childhood? (BE SPECIFIC - GET DETAILS)

_____

_____

13. What was the highest grade in school he/she completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL (POST COLLEGE EDUCATION):

SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

NONE - 00

DON'T KNOW - 98

14. The next part of this questionnaire concerns jobs that you have held.

I am interested in all the different kinds of work you have done for a period of one month or more. Please include summer jobs or part-time jobs you may have held while you were going to school.

First, are you currently employed, either full or part-time?

YES.....ASK A..... 1 →

NO.....ASK A..... 2 →

	14A. TITLE What is (was) your main title?	14B. DUTIES What are (were) your major duties on this job? PROBE.
CURRENT (MOST RECENT) JOB		

A. [IF YES] -- What is your present job title? ASK A-C. THEN SHOW CARD #14D. On this card is a list of exposures that might affect your health. Please tell me if you have been or are exposed to any harmful substance on your present job. RECORD IN COLUMN D. When did you start working at this job? RECORD IN COLUMN E.

[IF NO] -- What was your last job title? ASK A-C. THEN SHOW CARD #14D. On this card is a list of exposures that might affect your health. Please tell me if you were exposed to any harmful substance on your last job. RECORD IN COLUMN D. When did you start working at this job? RECORD IN COLUMN E. When was the ending date of your last job? RECORD IN COLUMN F.

What other types of jobs did you have since you were 16 years old, besides (your current/your most recent) job? RECORD ON CHART - ASK A-F.

14C. COMPANY What kind of company is (was) this? What type of industry was that in?	14D. EXPOSURES Which substances are (were) you exposed to?	14E. START DATE When did you start this job?		14F. END DATE When did this job end?	
		MONTH	YEAR	MONTH	YEAR

15. On this card (HAND CARD #15) is a list of exposures that might affect your health. Please tell me about these or other substances you think might have been harmful to which you may have been exposed either in a job, hobby, or any other situation. Please tell me if you have worked with or been exposed to any of these at least once a week for more than one month. Even though you may have mentioned them, please tell me again. RECORD IN CHART BELOW.

Exposure (RECORD SPECIFICS - FOR EXAMPLE: ON THE JOB, A HOBBY, ETC.)	When were you first exposed to this?		When was the last time you were exposed to this?	
	MONTH	YEAR	MONTH	YEAR

16. Other than the jobs you have just told me about, have you ever worked either for pay or not on a farm or other agricultural setting?

YES.....ASK A & B..... 1

NO.....SKIP TO Q17..... 2

A. When and where did you do this work?

B. What chemicals were you exposed to, chemicals such as insecticides, fungicides, herbicides, sprays or powders?

DATES	WHERE	CHEMICALS

17. How many times have you been unemployed, if ever?

RECORD # TIMES:_____

NEVER.....99

IF NEVER, SKIP TO Q17

A. What were the reasons for these periods of unemployment?

_____

_____

_____

_____

IF THE INTERVIEWEE IS CURRENTLY UNEMPLOYED (Q14) ASK THE FOLLOWING QUESTION.

18. How long have you been unemployed?

RECORD:_____

Now for some general questions.

19. About how many hours do you sleep each night?

RECORD HOURS:_____

A. Do you usually take a nap during the day?

YES..... 1

↳ How long do you usually sleep when you nap?

_____ / _____

MINUTES HOURS

NO..... 2

B. Compared to other people your age, would you say your health is:

Better,..... 1

About the same, or..... 2

Worse?..... 3

C. Is there anything about your health -- physical, emotional or mental -- that would limit the kind or amount of work or work around the house you can do?

YES..... 1

NO..... 2

20. HAND CARD 20 TO R Please look at this card and use the answers for the next set of questions.

	ALMOST EVERY DAY	SOME-TIMES	RARELY	NEVER
How often do you eat breakfast? Would you say:	1	2	3	4
How often do you eat between meals?	1	2	3	4
How often do you participate in active sports?	1	2	3	4
How often do you swim or take long walks?	1	2	3	4
How often do you work in the garden?	1	2	3	4
How often do you do physical exercises, jog or run?	1	2	3	4
How often do you take weekend automobile trips?	1	2	3	4
How often do you hunt or fish?	1	2	3	4

21. How many times have you been married?

RECORD # OF TIMES:_____

22. How many times have you been divorced?

RECORD # OF TIMES:_____

23. Have you ever been arrested?

YES.....ASK A..... 1
NO.....SKIP TO Q24..... 2

A. How many times?

RECORD # OF TIMES:_____

24. What were the dates of your military service?

ENTRY:_____/_____
MONTH YEAR

SEPARATION:_____/_____
MONTH YEAR

25. Did you enlist or were you drafted?

ENLISTED..... 1
DRAFTED..... 2

26. What were the locations of your military service? RECORD IN CHART BELOW. PROBE FOR COMPLETE LOCATION.

A. FOR EACH LOCATION, ASK: What was your company designation? PROBE FOR EACH LOCATION - RECORD IN COLUMN A OF CHART.

B FOR EACH LOCATION, ASK: When were you in (...)? Please give me the month and year of arrival and the month and year you left (...). INSERT LOCATION FOR (...) - RECORD MONTH/YEAR R ARRIVED AND LEFT LOCATION IN COLUMN B OF CHART.

C. What were your duties when you were in (...)? INSERT LOCATION FOR (...). ASK FOR EACH LOCATION - RECORD IN COLUMN C OF CHART - PROBE FULLY FOR DUTIES.

LOCATIONS	A. COMPANY DESIGNATION	B. DATES FROM MO/YR	B. DATES TO MO/YR	C. DUTIES
1.		___ 19___	___ 19___	
2.		___ 19___	___ 19___	
3.		___ 19___	___ 19___	
4.		___ 19___	___ 19___	
5.		___ 19___	___ 19___	

27. Were you in any areas where any defoliants or weedkillers were used, for example, around the camp, back pack or truck spraying or air spraying by helicopter or airplane?

YES.....ASK A..... 1

NO.....SKIP TO Q28..... 2

A. When, that is, what months and years did the defoliant and weedkiller spraying occur? RECORD DATES IN COLUMN A OF CHART.

B. Please give me the name of the location of where you were when the defoliants and weedkillers were sprayed. RECORD LOCATION FOR EACH DATE IN COLUMN B OF CHART.

C. Please tell me if the defoliants or weedkillers were used by back pack or truck spraying or by helicopter or airplane spraying? RECORD IN COLUMN C OF CHART FOR EACH DATE.

D. Give me the names of the defoliants and weedkillers that were used. RECORD IN COLUMN D OF CHART FOR EACH DATE.

A. DATES MONTH/YEAR	B. LOCATION	C. SOURCE OF SPRAYING	D. NAME OF AGENT
1. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
2. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
3. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
4. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	

28. Did you do <u>any</u> of the spraying yourself?

YES.....ASK A..... 1

NO.....SKIP TO Q29..... 2

A. What dates, month and year, did you do this spraying? RECORD IN COLUMN A OF CHART.

B. Please tell me where you did this spraying, the exact location. RECORD IN COLUMN B OF CHART FOR EACH DATE.

C Please tell me if the defoliants or weedkillers were used by back pack or truck spraying or helicopter or plane spraying? CODE IN COLUMN C OF CHART.

D. Tell me the names of the defoliants and weedkillers that you used. RECORD NAMES IN COLUMN D OF CHART.

A. DATES MONTH/YEAR	B. LOCATION	C. SOURCE OF SPRAYING	D. NAME OF AGENT
1. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
2. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
3. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
4. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	
5. ____ 19____		BACKPACK.....1 TRUCK.....2 HELICOPTER.....3 AIRPLANE.....4 OTHER (SPECIFY)..5 ↳_____	

29. Did you ever handle drums of defoliant, load spraying equipment, maintain, clean or repair spraying equipment or participate in clean up of spills or leaks?

YES.....ASK A.....1

NO.....SKIP TO Q30.....2

A. What dates, month and year, did you handle, clean, repair, etc. drums of defoliant, spraying, equipment, etc.? RECORD IN COLUMN A.

B. Where did you do this? What was the location? RECORD IN COLUMN B OF CHART FOR EACH DATE.

C. What did you actually do? RECORD FULLY FOR EACH DATE IN COLUMN C.

A. DATES MONTH/YEAR	B. LOCATION	C. DUTIES
1. ____ 19____		
2. ____ 19____		
3. ____ 19____		
4. ____ 19____		
5. ____ 19____		
6. ____ 19____		
7. ____ 19____		

30. Were you ever under a spraying operation while it was going on?

YES.....ASK A..... 1

NO.....SKIP TO Q31..... 2

A. Please give me the dates, month and year, when you were under a spraying operation while it was going on. RECORD DATES IN COLUMN A OF CHART.

B. Where did this take place, tell me the location. RECORD FOR EACH DATE IN COLUMN B OF CHART.

C. Please tell me in detail, the type of defoliants used, type of spraying and any other details regarding the spraying operation. RECORD FULLY IN COLUMN C OF CHART FOR EACH DATE.

A. DATES MONTH/YEAR	B. LOCATION	C. DETAILS OF OPERATION
1. ____ 19____		
2. ____ 19____		
3. ____ 19____		
4. ____ 19____		
5. ____ 19____		
6. ____ 19____		
7. ____ 19____		

31. Now I would like to know the closest contact <u>you</u> had with <u>any</u> spraying operation such as defoliants, insecticides, etc.

A. As I read each of the following plese tell me if you were ever: READ a-d AND CODE IN COLUMN A.

IF ALL "NO".....SKIP TO Q32 ALL OTHERS - INCLUDING D.K. - CONTINUE

B. Please give me the date, month and year, that you (think you) were (...). INSERT APPROPRIATE a-d FOR (...). RECORD IN COLUMN B OF CHART.

C. Where were you, in other words, what city, state or country were you in when you (thought you) were (...)? INSERT a-d FOR (...). RECORD LOCATION R WAS AT IN COLUMN C OF CHART.

D. At the time you (thought you) were (...) was the spraying operation being done by back pack, truck, airplane, helicopter spraying, or some other way. INSERT a-d FOR (...) - CODE IN COLUMN D.

E. Please tell me the kind of defoliants, insecticides or sprays being used when you were (...)? INSERT a-d FOR (...) - CODE IN COLUMN E.

	A. YES	NO	D.K.	B. DATES	C. LOCATION	D. SOURCE OF SPRAYING	E. KIND
a. Drenched with spray?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 ↳_____	
b. Directly under spray but not drenched?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 ↳_____	
c. One who did the spraying?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 ↳_____	
d. Nearby spraying but not directly under?	1	2	9	MO: _____ YR: 19____		BACKPACK....1 TRUCK.....2 AIRPLANE....3 HELICOPTER..4 OTHER(SPEC).5 ↳_____	

32. Were you exposed to "Agent Orange" while you served in Vietnam?

YES.....ASK A..... 1
NO.....SKIP TO Q33..... 2
NOT SURE.....ASK A..... 3
DON'T KNOW.....ASK A..... 9

A. (Even though you're not sure) When do you think you were exposed to "Agent Orange?" Please give me the month and year?

RECORD DATE: _____ / _____
MONTH YEAR

B. Where were you, what area of Vietnam, when you were exposed?

RECORD LOCATIONS:

1. _____

2. _____

3. _____

C. Can you describe that experience?

_____

_____

_____

D. Do you think you were exposed to <u>anything else</u> while in Vietnam that could have affected your health?

YES.....ASK a..... 1
NO.....SKIP TO Q33..... 2

a. Please explain that.

_____

_____

_____

_____

33. Please look at this card (HAND CARD #33) and give me the letter that comes closest to your income last year before taxes. Please include all sources, for example, wages, dividends, rentals, welfare, disability, etc.

A.	LESS THAN $3,000.....01	I.	$12,000 - $13,999.....09
B.	$3,000 - $3,999.....02	J.	$14,000 - $16,999.....10
C.	$4,000 - $4,999.....03	K.	$17,000 - $19,999.....11
D.	$5,000 - $5,999.....04	L.	$20,000 - $24,999.....12
E.	$6,000 - $6,999.....05	M.	$25,000 - $29,999.....13
F.	$7,000 - $8,499.....06	N.	$30,000 - $39,999.....14
G.	$8,500 - $9,999.....07	O.	$40,000 - $49,999.....15
H.	$10,000 - $11,999.....08	P.	$50,000 AND OVER.....16

REFUSED.....97
DON'T KNOW.....98

34. Do you own or rent your home (apartment)?

OWN..... 1
RENT..... 2
SOMETHING ELSE..... 3
→ SPECIFY:_____

35. We want to thank you for all the time you have given us. Your cooperation in this important study is vital to the success of the project. To complete our objectives in documenting your health status and health history we would like to contact the various hospitals, doctors or health care services you have mentioned in this interview so that we can look at your medical records. In order for us to do so, we need a signed release from you indicating your willingness to allow your medical records be made available to us. All information we collect will be kept strictly confidential and will be used for statistical and research purposes only. Your name or any details of your medical history will not be revealed. Are you willing to sign such a release?

YES.....GIVE CONSENT FORM

NO.....THANK AND TERMINATE

CONSENT FOR RELEASE OF MEDICAL RECORD INFORMATION

I hereby authorize the release of any medical records and information regarding my diagnosis and treatment to the investigators for the "Agent Orange Study."

_____ _____

SIGNATURE DATE

SOCIAL SECURITY # _____ _____ _____

SERVICE RECORD # _____

INTERVIEWER SIGNATURE_____

DATE:_____

CARD #14-15

A. CHEMICALS, CLEANING FLUIDS OR SOLVENTS (SPECIFY)

B. ASBESTOS, INSULATION MATERIAL

C. INSECTICIDES

D. PLASTICS OR RESINS (SPECIFY)

E. X-RAYS

F. ANESTHETIC GASES

G. RADIOACTIVITY, ISOTOPES

H. PETROLEUM PRODUCTS, FUELS, BENZENE (SPECIFY)

I. LEAD OR METAL SMELTING FUMES (SPECIFY)

J. HERBICIDES (PLANT KILLERS)

CARD #20

ALMOST EVERY DAY

SOMETIMES

RARELY

NEVER

CARD #33

A. LESS THAN $3,000

B. $3,000 - $3,999

C. $4,000 - $4,999

D. $5,000 - $5,999

E. $6,000 - $6,999

F. $7,000 - $8,499

G. $8,500 - $9,999

H. $10,000 - $11,999

I. $12,000 - $13,999

J. $14,000 - $16,999

K. $17,000 - $19,999

L. $20,000 - $24,999

M. $25,000 - $29,999

N. $30,000 - $39,999

O. $40,000 - $49,999

P. $50,000 AND OVER

CASE ID#: _____

_____

TIME: _____ START _____ END

INTERVIEWER: _____

VETERANS MEDICAL HISTORY

MEDICAL HISTORY QUESTIONNAIRE

1. First let's start with some questions about the health of your relatives. Have any of the follwoing conditions occurred in your blood relatives? By blood relatives we mean brothers, sisters, grandparents, aunts and uncles with at least one parent in common. Have any of your blood relatives had:

	NO	YES	RELATIONSHIP TO RESP.
Heart disease?	1	2	
High blood pressure?	1	2	
Lung disease?	1	2	
Stroke?	1	2	
Asthma?	1	2	
Kidney disease?	1	2	
Liver disease?	1	2	
Diabetes?	1	2	
Mental or nerve disorders?	1	2	
Cancer or tumors?	1	2	
→ What type?_____			

2. Are your natural parents alive?

	YES	NO	Current age or age at death
Father.....			
Mother.....			

IF BOTH PARENTS ARE ALIVE, SKIP TO Q4
IF ONE OR BOTH DECEASED, CONTINUE WITH Q3

3. What did your natural (mother/father) die from?

	FATHER	MOTHER
Heart Attack.....	_____	_____
Heart Failure.....	_____	_____
High Blood Pressure....	_____	_____
Lung Disease.....	_____	_____
Stroke.....	_____	_____
Cancer or Tumor.....	_____ Specific site: _____	_____ Specific site: _____
Kidney Disease.....	_____	_____
Liver Disease.....	_____	_____
Diabetes.....	_____	_____
Accident or war.....	_____	_____
Pneumonia.....	_____	_____
Old Age.....	_____	_____
Asthma.....	_____	_____
Other.....	_____	_____

SPECIFY:

_____

4. Were you ever wounded in combat during your time in the service?

YES..... 1
NO.....SKIP TO Q5..... 2

A. In what years were you wounded?

RECORD:_____

B. What part(s) of you was (were) injured? CODE ALL MENTIONS.

HEAD..... 1
FACE..... 2
CHEST..... 3
ABDOMEN..... 4
LIMBS..... 5

C. What type of injury was it? Was it a: CODE ALL MENTIONS.

Bullet wound,..... 1
Schrapnel,..... 2
Knife wound, or..... 3
Impact trauma?..... 4
OTHER..... 5
→SPECIFY:_____

5. Were you hospitalized for any reason other than a combat wound while in the service?

YES..... 1
NO.....SKIP TO Q6..... 2

A. What was the problem?

_____

B. When were you hospitalized?

DATE:_____

C. Where were you hospitalized?

_____

D. Did the disease/condition completely resolve?

YES.....SKIP TO Q6..... 1
NO..... 2

E. Could you explain that?

_____

_____

_____

6. While serving in South Vietnam were you treated in a medical facility for any condition which did not require hospitalization?

YES..... 1

NO.....SKIP TO Q7..... 2

A. What were you treated for?

_____

_____

_____

B. When?

DATE(S):_____

_____

7. Have you ever been seriously injured other than in combat? (Serious injury means broken bone, or an injury requiring hospital admission, or injury causing significant disability.)

YES..... 1

NO.....SKIP TO Q8..... 2

A. What type of injury was that? RECORD IN "A" BELOW.

B. How did it occur? RECORD IN "B" BELOW.

C. In what year did it occur? RECORD IN "C" BELOW.

A. INJURY	B. MODE OF INJURY	C. YEAR OF INJURY
1.		
2.		
3.		
4.		

8. Have you ever had any surgical operations?

YES..... ASK A..... 1

NO.....SKIP TO Q9..... 2

A. What type of surgical operations were they? RECORD IN CHART BELOW.

B. Please give me the name and address, city and state, of the hospital where (...) surgery was performed. INSERT TYPE OF SURGERY FOR (...). RECORD FULL ADDRESS IN COLUMN B OF CHART.

C. When did the surgery take place? RECORD MONTH AND YEAR IN COLUMN C OF CHART.

A. TYPE OPERATION	B. NAME/ADDRESS OF HOSPITAL	C. DATE
1.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
2.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
3.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
4.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
5.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
6.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
7.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____
8.	NAME:_____ ADDRESS:_____ CITY:_____ STATE:_____	MO:_____ YR:_____

9. Have you ever been admitted to a hospital for any other reason besides an injury or surgical operation?

YES..... 1

NO.....SKIP TO Q10..... 2

A. Please tell me the hospital, their address, including the city and state, the year, and the relevant condition that you were admitted for.

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

HOSPITAL:_____ CONDITION:_____

ADDRESS:_____ _____

YEAR:_____ _____

10. Are you taking any prescribed medicines now, i.e. in the last month?

YES..... 1
NO.....SKIP TO Q11..... 2

A. Could you tell me the medicines and the reason you take them?

MEDICATION	CONDITION
1.	1.
	2.
3.	3.

11. Have you ever regularly used any medication or drugs for three months at a time or longer?

YES.....ASK A & B..... 1

NO.....SKIP TO Q12..... 2

A. What were/are they?

B. What were they for?

A. NAME	B. CONDITION

Did you ever take any drugs or pills to prevent malaria, prevent or treat tuberculosis, or treat fungal diseases?

YES..... 1
NO.....SKIP TO Q13..... 2

A. What were they for? CODE ALL MENTIONS.

MALARIA..... 1
TUBERCULOSIS..... 2
FUNGUS..... 3

B. What was (were) the name(s) of the drug(s)?

_____

_____

13. Have you had any infections (ear, nose, skin, eye) in the last year?

YES..... 1
NO.....SKIP TO Q15..... 2

A. How many?

RECORD #:_____

14. Have you ever had trouble with the healing of a wound or lesion?

YES..... 1
NO.....SKIP TO Q15..... 2

A. What was the site and nature of the wound or lesion?

_____

Have you ever regularly smoked cigarettes for at least three months?

YES..... 1
NO.....SKIP TO Q25..... 2

16. Do you smoke cigarettes now? Please include little cigars or brown cigarettes.

YES..... 1
NO.....SKIP TO Q18..... 2

A. On the average, do you smoke more than one cigarette per day?

YES (REGULAR SMOKER)..... 1
NO (OCCASIONAL SMOKER)...SKIP TO Q18.... 2

17. At the present time, what is the average number of cigarettes you smoke per day?

RECORD #:_____

18. How old were you when you began smoking cigarettes regularly?

RECORD AGE:_____

19. What is the average number of cigarettes you smoked per day since you began to smoke/when you smoked? Please give your best estimate.

RECORD #:_____

What is the maximum number of cigarettes you ever smoked per day for as long as a year?

RECORD #:_____

NEVER SMOKED FOR
ONE YEAR.....SKIP TO Q23.....97

21. For how many years did you smoke this number of cigarettes per day?

RECORD YEARS:_____

REFER TO Q16

IF R NOT SMOKING NOW...SKIP TO Q23
ALL OTHERS.....CONTINUE

22. Have you ever attempted to stop smoking?

YES..... 1
NO.....SKIP TO Q25..... 2

A. What is the longest time you were able to stop?

RECORD #:_____ DAYS
_____ WEEKS
_____ MONTHS
_____ YEARS

23. How old were you when you stopped smoking cigarettes regularly?

RECORD AGE:_____

24. What was the main reason you stopped smoking?

HEALTH..... 1
ADVERSE PUBLICITY..... 2
OTHER..... 3
→SPECIFY:_____

25. Have you ever regularly smoked pipes or cigars for at least three months?

YES..... 1
NO.....SKIP TO Q37..... 2

26. Do you smoke pipes or cigars now?

YES..... 1
NO.....SKIP TO Q27..... 2

A. On the average, do you smoke at least one pipeful or cigar each day?

YES (REGULAR)..... 1
NO (OCCASIONAL)..... 2

27. Which do/did you smoke?

PIPE..... 1
CIGAR..... 2
BOTH..... 3

REFER TO Q26

IF R NOT SMOKING NOW...SKIP TO Q29
ALL OTHERS.....CONTINUE

28. At the present time how many pipefuls or cigars do you usually smoke per day?

RECORD #:_____

DON'T SMOKE DAILY.....97

29. How old were you when you began smoking pipes or cigars regularly?

RECORD AGE:_____

30. What is the average number of pipefuls or cigars you smoked per day since you began to smoke/when you smoked? Please give your best estimate.

RECORD #:_____

31. What is the maximum number of pipefuls or cigars you ever smoked per day for as long as a year?

RECORD #:_____

NEVER SMOKED FOR
ONE YEAR.....SKIP TO Q33.....97

32. For how many years did you smoke this number of pipefuls or cigars per day?

RECORD YEARS:_____

REFER TO Q26

IF R NOT SMOKING NOW...SKIP TO Q35
ALL OTHERS.....CONTINUE

33. Have you ever attempted to stop smoking?

YES..... 1
NO.....SKIP TO Q37..... 2

34. What is the longest time you were able to stop?

RECORD #:_____ DAYS
_____ WEEKS
_____ MONTHS
_____ YEARS

35. How old were you when you stopped smoking?

RECORD AGE:_____

36. What was the main reason you stopped smoking?

HEALTH..... 1
ADVERSE PUBLICITY..... 2
OTHER..... 3
→ SPECIFY:_____

37. Now let's talk about drinking alcoholic beverages, that is beer, wine, or mixed drinks. Did you ever drink alcoholic beverages on a fairly regular basis?

YES..... 1

NO.....SKIP TO Q39..... 2

A. When did you start drinking alcoholic beverages on a fairly regular basis?

RECORD:_____ DATE

OR

_____ AGE

B. Do you currently drink alcoholic beverages on a fairly regular basis?

YES.....SKIP TO Q38..... 1

NO..... 2

C. When did you last drink on a fairly regular basis?

RECORD:_____ DATE

OR

_____ AGE

38. You said that you (last drank on a fairly regular basis in DATE/are currently drinking on a fairly regular basis). How often did you drink alcohol during the last 3 months (that you did drink)? Would you say:

Every day,..... 6
4 to 6 days a week,..... 5
2 or 3 days a week,..... 4
Once a week,..... 3
2 or 3 days a month, or..... 2
Once a month?..... 1

A. On the days that you (drink/drank) about how many drinks (do/did) you have per day? That is, how many shots, cans or glasses?

RECORD #:_____ SHOTS
CANS
GLASSES

B. During the last three months (that you drank) which one of the following beverages did you drink most? Would you say:

Hard liquor,..... 1
Beer or ale, or..... 2
Wine or champagne?..... 3

39. Have you ever smoked marijuana regularly for a period of at least one month?

YES..... 1

NO.....SKIP TO Q41..... 2

A. When did you start smoking marijuana on a fairly regular basis?

RECORD DATE: ____/____
MONTH YEAR

B. These days, do you smoke marijuana fairly regularly?

YES..... 1

NO..... 2

IF "YES" TO Q39B - ENTER [0][0] [0][0] IN BOX OF Q39C
AND SKIP TO Q40

IF "NO" TO Q39B - ASK Q39C

C. When did you last smoke marijuana on a fairly regular basis?

RECORD DATE: [ ][ ] [ ][ ]
MO. YR.

40. You said that you (last smoked marijuana on a fairly regular basis in (END DATE)/are currently smoking marijuana on a fairly regular basis). HAND CARD #40 Please look at this card and tell me which category best describes how often you smoked marijuana during the last three months (that you smoked on a fairly regular basis)?

EVERY DAY..... 6
4 TO 6 DAYS A WEEK..... 5
2 OR 3 DAYS A WEEK..... 4
ONCE A WEEK..... 3
2 OR 3 DAYS A MONTH..... 2
ONCE A MONTH..... 1

A. HAND CARD #40A On the days that you smoked marijuana, about how many joints did you smoke per day?

LESS THAN ONE A DAY..... 1
1 OR 2 A DAY..... 2
3 OR 4 A DAY..... 3
5 OR 6 A DAY..... 4
7 OR 8 A DAY..... 5
9 OR 10 A DAY..... 6
MORE THAN 10 A DAY..... 7
→HOW MANY?_____

Have you ever used barbiturates regularly for a period of at least one month? You might know barbiturates as "barbs," "downers," Nembutol, Seconal, Amytol, Doriden, Quaalude, Methaqualone, "Sopors," Reds, Rainbows, or Yellow Jackets?

YES..... 1

NO.....SKIP TO Q42..... 2

A. When did you start using barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use barbiturates?

YES.....SKIP TO Q42..... 1

NO..... 2

C. When did you last use barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

42. Have you ever used amphetamines regularly for a period of at least one month? You might know amphetamines as "dexies," "uppers," "bennies," "diet pills," "speed," "crystals," methedrine, Benzadrine or Dexadrine.

YES..... 1

NO.....SKIP TO Q43..... 2

A. When did you start using amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use amphetamines?

YES.....SKIP TO Q43..... 1

NO..... 2

C. When did you last use amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

Have you ever used opiates regularly for a period of at least one month? You might know opiates as heroin, morphine, opium, codeine.

YES..... 1
NO.....SKIP TO Q44..... 2

A. When did you start using opiates?

RECORD: [ ][ ] [ ][ ]
MO. YR.

B. Do you still use opiates?

YES.....SKIP TO Q44..... 1
NO..... 2

C. When did you last use opiates?

RECORD: [ ][ ] [ ][ ]
MO. YR.

44. Have you ever used cocaine regularly for a period of at least one month?

YES..... 1
NO.....SKIP TO Q45..... 2

A. When did you start using cocaine?

RECORD: [ ][ ] [ ][ ]
MO. YR.

B. Do you still use cocaine?

YES.....SKIP TO Q45..... 1
NO..... 2

C. When did you last use cocaine?

RECORD: [ ][ ] [ ][ ]
MO. YR.

45 Have you <u>ever</u> used intravenous drugs, "shot up?"

YES.....ASK A..... 1
NO.....SKIP TO Q46..... 2

A. Which ones?

1._____

2._____

3._____

B. Did you start using intravenous drugs <u>before</u> or <u>after</u> you served in Vietnam?

BEFORE..... 1
AFTER..... 2
DURING..... 3

C. Do you <u>still</u> use them?

YES..... 1
NO..... 2

D. Did you <u>ever</u> share needles?

YES..... 1
NO..... 2

... have you ever had any changes in weight that were of concern to you?

YES..... 1

NO..... 2

A. Have you <u>ever</u> had a weight change of more than 15 lbs. in six months?

YES..... 1

NO.....SKIP TO Q49..... 2

B. Was it because you were dieting?

YES..... 1

NO..... 2

C. Was it a:

	NO	YES	D. What year did this occur?	E. Is it a current problem?	
				YES	NO
a. Weight gain?.....	2 ASK b	1 ASK D→	——————→	1	2
b. Weight loss?.....	2	1 ASK D→	——————→	1	2

47. Did you seek medical care for this weight change?

YES..... 1

NO.....SKIP TO Q49..... 2

8 Where did you go for medical care regarding your weight change? Was it the

Military medical service, or.....SKIP TO Q49.....	1
A private doctor/ hospital?.....ASK A.....	2

A. Please give me the name and address, the city and state, of the Doctor and/or Hospital you went to regarding your weight change.

_____

_____

_____

_____

49. Now, I would like to ask you some questions about your skin?

A. (HAND CARD #49) Please look at this card and as I read the following, please tell me if you have ever had any problems with your skin? First: READ a-h AND CODE IN COLUMN A OF CHART.

IF NO TO ALL CONDITIONS.....SKIP TO Q50 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" IN COLUMN A - ASK: What year did this first occur? RECORD IN COLUMN B OF CHART.

C. Is the (...) a current problem or not? INSERT SKIN CONDITION R HAD/HAS IN COLUMN A FOR (...) - CODE ANSWER IN COLUMN C OF CHART.

D. Did you see a doctor about the (...) condition? INSERT CONDITION FOR (...) - CODE IN COLUMN D OF CHART.

IF R SAW A DOCTOR.....CONTINUE WITH E & F ALL OTHERS.....GO TO NEXT CONDITION

E. Where did you go for medical diagnosis and care for the (...) condition? Was it the Military Medical Service or a private doctor or hospital? INSERT CONDITION FOR (...) - RECORD IN COLUMN E OF CHART.

F. IF OTHER DOCTOR/HOSPITAL (NOT MILITARY) ASK: Please give me the name and address, city and state, of the doctor or hospital you went to for the diagnosis and care you received for the (...) condition. RECORD IN COLUMN F OF CHART.

A. CONDITION			B. YEAR OCCURRED	C. CURRENT		D. SEE DOCTOR		E. WHAT DOCTOR	F. NAME/ADDRESS
	YES	NO		YES	NO	YES	NO		
a. Eczema	1	2	19____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
b. Psoriasis	1	2	19____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
c. Recurrent Pimples/ Boils	1	2	19____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	

d. Recurring rashes	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
e. Persistant rashes for longer than a month	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
f. Skin Cancer	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
g. Porphyria Cutanea Tarda	1	2	19_____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
h. Other Problems SPECIFY:									
_____	1	2	19_____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	
_____	1	2	19_____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	

50. Have you ever had acne?

YES..... 1
NO.....SKIP TO Q52..... 2

51. Have you ever had severe acne?

YES.....ASK A..... 1
NO.....SKIP TO Q52..... 2

A. In what year did you first have this severe acne?

RECORD:_____

If you had recurrences of severe acne in what years did these begin?

19__ __, 19__ __, 19__ __

NEVER HAD RECURRENCES.....99

B. Which parts of your body were affected by the severe acne? Was it your:

	YES	NO
Face?.....	1	2
Temples?.....	1	2
Behind or in ears?....	1	2
Shoulders?.....	1	2
Trunk?.....	1	2
Elsewhere?.....	1	2
→ SPECIFY:_____		
_____		

C. For how long did you have severe acne? Would you say:

Less than a month,..... 1
1-6 months,..... 2
7-12 months,..... 3
1-5 years, or..... 4
More than 5 years?..... 5

D. Is the acne still a problem?

YES..... 1
NO..... 2

52. Does your skin sunburn easily?

YES..... 1
NO..... 2

A. About how many times a year do you get a severe sunburn?

RECORD # TIMES:_____

53. Have you ever noticed any change in skin color apart from jaundice or suntan?

YES.....ASK A..... 1
NO.....SKIP TO C..... 2

A. In what year did you notice this change?

RECORD: 19 _____

B. Could you describe the change in skin color? Was it:

	YES	NO
Dark patches on your face?.....	1	2
Dark patches on your trunk or limbs?.	1	2
Light patches on your face?.....	1	2
Light patches on your trunk or limbs?	1	2

C. Have you noticed any change in the sensitivity of your skin to sunlight?

YES..... 1
NO.....SKIP TO Q54..... 2

D. In what way has your skin's sensitivity changed? Has it:

Increased, or..... 1
Decreased in sensitivity?..... 2

E. In what year did this change start?

RECORD: 19 _____

54. Apart from normal balding have you ever noticed a change in the hairiness of your head or body?

YES..... 1

NO.....SKIP TO Q55..... 2

A. What was the change? Was it:

	YES	NO
Unusual loss on head?.....	1	2
Unusual general loss?.....	1	2
Increase on face/neck?.....	1	2
General increase?.....	1	2

B. In what year did the change in hairiness first occur?

RECORD: 19 _____

55. Have you ever had deafness or trouble hearing? Do not include problems during upper respiratory tract infection.

YES.....ASK A..... 1

NO.....SKIP TO Q56..... 2

A. When did you first have trouble hearing?

RECORD: 19 _____

B. Have you ever consulted a doctor about your loss of hearing?

YES..... 1

NO..... 2

C. Where did you receive your diagnosis and care for your hearing? Was it:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

56. Has there been a time when you had eye or eyelid infections or conjunctivitis (pink eye), more frequently than you would have expected?

YES..... 1
NO.....SKIP TO Q57..... 2

A. In what year did you <u>first</u> have these eye problems?

RECORD: 19 _____

B. Have you ever consulted a doctor about your eye problems?

YES.....ASK C..... 1
NO.....SKIP TO Q57..... 2

C. Where did you receive your diagnosis and care for your eyes? Was it:

A Military Medical Service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

Have you ever been troubled by recurrent or persistent headaches over a period of time longer than a month?

YES..... 1

NO.....SKIP TO Q58..... 2

A. Have these been diagnosed as migraines?

YES..... 1

NO..... 2

B. How bad are/were your headaches in general? Were they:

Severe enough to prevent usual activity,..... 1

Moderate but you were able to continue, or..... 2

Mild - easily relieved?..... 3

C. When you have a headache do you have other symptoms?

YES..... 1

NO.....SKIP TO G..... 2

D. What symptoms were the headaches associated with? Would you say:

	YES	NO
Flashes before the eyes?.....	1	2
Vomiting or nausea?.....	1	2
Numbness or tingling?.....	1	2
Sensitivity to bright light?.....	1	2
Dizziness (spinning)?.....	1	2
Faintness?.....	1	2
Blurring of vision?.....	1	2
Weakness on one side of the body?	1	2

E. Are the headaches associated with sensations which have not been mentioned?

YES..... 1

NO.....SKIP TO G..... 2

F. What are they?

_____

_____

G. Where do/did you feel the headache, mainly? Is/was it in the:

	YES	NO
Front of your head?.....	1	2
Back of your head?.....	1	2
Left side?.....	1	2
Right side?.....	1	2
All over or around the head?.....	1	2

H. About what year were you first troubled by recurring headaches?

RECORD: 19 _____

I. Do you still have problems with headaches?

YES..... 1
NO..... 2

J. Have you ever consulted a doctor about these headaches?

YES..... 1
NO.....SKIP TO Q58..... 2

K. Where did you receive your diagnosis and care for headaches? Was it:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

58. The next set of questions is about your heart and circulation.

A. Please look at this card (HAND CARD #58) and as I read each of the following tell me if you have ever had the condition or not. Have you had: READ a-j AND CODE IN COLUMN A OF CHART.

IF NO CONDITIONS...SKIP TO Q59 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) first occur? INSERT CONDITION FOR (...) - RECORD IN COLUMN B OF CHART.

C. Is the (...) a current problem? INSERT PROBLEM FOR (...) - CODE IN COLUMN C OF CHART.

D. Did you see the Military Medical Service or a private doctor or hospital for the diagnosis and care for your (...)? INSERT PROBLEM FOR (...) - CODE IN COLUMN D OF CHART.

A. CONDITION	EVER HAD YES	EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE
a. Heart attack	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
b. Angina	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
Heart failure	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
d. High blood pressure	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
e. Rheumatic fever	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
f. Disorders of the heart valves	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
g. Congenital heart disease	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
h. Clots in legs	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
i. Swelling of the ankles	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2
j. Other heart conditions (SPECIFY) _____	1	2	19 ____	1	2	Military/Medical...GO TO F....1 Doctor/Hospital....ASK E.....2

E. IF PRIVATE DOCTOR OR HOSPITAL, ASK: What is the name, address, city and state of the doctor/hospital you saw for diagnosis and care of (...)? RECORD IN COLUMN E OF CHART.

F. Are you currently under the care of a Military Medical Service or a private doctor or hospital for (...)? RECORD IN COLUMN F OF CHART.

G. IF PRIVATE DOCTOR/HOSPITAL: What is the name, address, city and state of the doctor/hospital you are currently under care for (...)? RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS/CITY/STATE	F. CURRENT CARE	G. NAME/ADDRESS/CITY/STATE CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

59. Have you ever had pain in the center of your chest which lasted longer than 30 minutes at a time?

YES..... 1
NO.....SKIP TO Q60..... 2

A. In what year did you first experience this chest pain?

RECORD: 19 _____

B. Has this chest pain recurred?

YES..... 1
NO.....SKIP TO Q60..... 2

C Do you still experience this chest pain?

YES..... 1
NO.....SKIP TO Q60..... 2

D. Was/is chest pain brought on by any of the following:

	YES	NO
Walking on flat ground, up hills, on exertion like running?.....	1	2
Deep breathing or coughing?.....	1	2
Eating?.....	1	2
Change in position, e.g. stooping?.....	1	2
Other?.....	1	2
→ SPECIFY:_____		

E. Was/is chest pain associated with:

	YES	NO
Shortness of breath?.....	1	2
Sweating?.....	1	2
Feeling of tightness or pressure?.....	1	2
Breathing?.....	1	2
Pain in either arm?.....	1	2
Pain in jaw?.....	1	2
Other?.....	1	2
→ SPECIFY:_____		

60. Have you ever suffered from palpitations (unpleasant sensation of your heart beating)?

YES..... 1
NO.....SKIP TO Q61..... 2

A. In what year did the palpitations first occur?

RECORD: 19 _____

B. Do you still get palpitations?

YES..... 1
NO..... 2

C. Do/did the palpitations occur with:

	YES	NO
Exertion?.....	1	2
Emotion?.....	1	2

D. On some occasions did you feel that your heart:

	YES	NO
Missed beats?.....	1	2
Became irregular?.....	1	2
Beat slowly?.....	1	2
Beat very quickly?.....	1	2

61. Have you ever had shortness of breath or difficulty with breathing?

YES..... 1

NO.....SKIP TO Q62..... 2

A. When does this difficulty occur? Is it:

	YES	NO
On walking up a hill or flight of stairs?.....	1	2
On breathing in irritating air or substances?.....	1	2
At rest?.....	1	2
With wheezing?.....	1	2
Does it wake you at night?.....	1	2
Other?.....	1	2
SPECIFY: _____		

B. In what year did you first have difficulties with breathing?

RECORD: _____

C. Do you still have difficulty with breathing?

YES..... 1

NO..... 2

D. How do/did you relieve your shortness of breath? By:

	YES	NO
Taking medicine?.....	1	2
Resting?.....	1	2
Sitting upright?.....	1	2
Other?.....	1	2
SPECIFY: _____		

62. Have you suffered from:

	YES	NO
Varicose veins?.....	1	2
Pains in legs on walking any distance?.....	1	2

A. Have you seen a doctor about these symptoms?

YES..... 1

NO.....SKIP TO Q63..... 2

B. Where did you receive your diagnosis and care for these symptoms? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

63. The next set of questions is about respiratory problems.

(HAND CARD #63) Please look at this card and as I read the following, please tell me if you have had had any of these conditions. READ a-m AND CODE IN COLUMN A OF CHART.

IF NO TO ALL...SKIP TO Q64 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did (...) first occur? INSERT PROBLEMS FOR (...) - RECORD IN COLUMN B OF CHART.

C. Is (...) a current problem? INSERT PROBLEM FOR (...) - RECORD IN COLUMN C OF CHART.

D. Are you on medication for your (...)? INSERT PROBLEM FOR (...) - RECORD IN COLUMN D OF CHART.

E. Did you see a Military Medical Service or a private doctor or hospital for diagnosis and care for your (...)? INSERT PROBLEM FOR (...) - RECORD IN COLUMN E OF CHART.

F. IF OTHER DOCTOR OR HOSPITAL SEEN FOR DIAGNOSIS OR CARE, ASK: What is the name, address, city and state of the doctor/hospital you saw for diagnosis and care? RECORD NAME AND ADDRESS IN COLUMN F.

A. PROBLEM	EVER HAD YES	EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. TAKE MEDICATION YES	D. TAKE MEDICATION NO	E. DIAGNOSIS AND CARE	F. NAME/ADDRESS/CITY/STATE
a. Sinusitis?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
b. Frequent nose bleeds?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
c. Frequent colds? (more than 3 a year)	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
d. Asthma?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
e. Chronic bronchitis?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
f. Emphysema?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	

g. T.B.?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
h. Bronchiectasis?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
i. Pleurisy?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
j. Pneumonia?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
k. Pneumonia more than once?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
l. Cancer of the lung?	1	2	19 ____	1	2	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK F.....2	
m. Other lung disease(s)? SPECIFY:									
_____	1	2	19 ____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	
_____	1	2	19 ____	1	2	1	2	Mil/Medical.....1 Doctor/Hosp..ASK F.....2	

64. Do you usually cough first thing in the morning in bad weather?

YES..... 1
NO..... 2

65. Do you usually cough at other times during the day and night in bad weather?

YES..... 1
NO..... 2

66. Do you cough first thing in the morning (when you get up) on more than 50 days in a year?

YES..... 1
NO.....SKIP TO Q69..... 2

67. For how many years have you had this cough? Would you say:

Less than 2 years,..... 1
2 to 5 years,..... 2
6 to 10 years, or..... 3
More than 10 years?..... 4

68. Do you usually bring up phlegm, sputum, or mucous from your chest first thing in the morning in bad weather?

YES..... 1
NO..... 2

69. Do you usually bring up phlegm, sputum, or mucous from your chest at other times during the day or night in bad weather?

YES..... 1
NO..... 2

70. Do you usually bring up phlegm from your chest first thing in the morning on more than 50 days in a year?

YES..... 1
NO.....SKIP TO Q72..... 2

71. For how many years have you raised phlegm, sputum, or mucous from your chest? Would you say:

Less than 2 years,..... 1
2 to 5 years,..... 2
6 to 10 years, or..... 3
More than 10 years?..... 4

72. In the past three years, have you had a period of increased cough and phlegm lasting for three weeks or more?

YES..... 1
NO.....SKIP TO Q74..... 2

73. Have you had more than one such three-week period?

YES..... 1
NO..... 2

74. Does your breath ever sound wheezing or whistling?

YES..... 1
NO.....SKIP TO Q76..... 2

75. On how many days has this happened during the past year?

RECORD # DAYS:_____

76. Have you ever had attacks of shortness of breath with wheezing?

YES..... 1
NO..... 2

77. During the past three years, how much trouble have you had with illnesses such as chest colds, bronchitis, or pneumonia? Would you say you have had a:

Great deal of trouble,..... 1
Some trouble, or..... 2
No trouble?.....SKIP TO Q79..... 3

78. During the past three years, how often were you unable to do your usual activities because of illness, such as chest colds, bronchitis, or pneumonia? Would you say:

Once,..... 1
Two to five times,..... 2
More than five times in the past three years, or..... 3
Never?..... 4

79. Have you ever had a diagnosis of diabetes?

YES..... 1
NO.....SKIP TO Q80..... 2

A. At what age was it diagnosed?

RECORD AGE:_____

B. Where did you receive your diagnosis and care for diabetes? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

C. What is your current treatment? Is it:

	YES	NO
Diet?.....	1	2
Pills?.....	1	2
Insulin?.....	1	2
Nothing?.....	1	2

80. Have you ever had a diagnosis of thyroid trouble?

YES..... 1
NO.....SKIP TO Q81..... 2

A. Was this hypo- or hyperthyroid trouble?

HYPOTHYROID..... 1
HYPERTHYROID..... 2
DON'T KNOW..... 8

B. Did you seek medical care for the thyroid trouble?

YES..... 1
NO.....SKIP TO Q81..... 2

C. Where did you receive your diagnosis and care for your thyroid trouble? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

81. Has a doctor ever told you that you have gout?

YES..... 1

NO.....SKIP TO Q82..... 2

A. Where did you receive your diagnosis and care for your gout? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

82. Next, some questions regarding gastrointestinal conditions.

(HAND CARD #82) Please look at this card and as I read each of the following, please tell me if you have ever had any of these problems. READ a-1 AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL CONDITIONS...SKIP TO Q83 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) condition first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Do you have the (...) condition currently? RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or a private doctor or hospital for this (...) condition? CODE APPROPRIATE ANSWER IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR OR HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for the (...) condition. RECORD IN COLUMN E OF CHART.

CONDITIONS	A. YES	A. NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS/CITY/STATE DOCTOR/HOSPITAL
a. Esophagitis?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Hiatus hernia?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Gastric or duodenal ulcer?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Crohns disease or regional ileitis?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Bowel obstruction?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	

f. Di[illegible]iculitis?	1	2	19_____	1	2	[illegible]il/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Spastic or irritable colon?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
h. Ulcerative colitis?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
i. Anal problems or hemorrhoids?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
j. Dysentery?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
k. Malabsorption?	1	2	19_____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
l. Other gastro intes-tinal conditions? (SPECIFY) _____	1	2	19_____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	
_____	1	2	19_____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

83. (HAND CARD #83) Please look at this card and a(read the following, please tell me if you ever h(ny of these problems. READ a-g AND RECORD IN COLU(OF CHART.

IF "NO" TO ALL...SKIP TO Q84
ALL OTHERS.....CONTINUE

B. In what year did (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or private doctor or hospital for the diagnosis and care of the (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR OR HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for the (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS OF DOCTOR/HOSPITAL IN COLUMN E OF CHART.

CONDITION	A. YES	A. NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS/CITY/STATE
a. Persistant indigestion or abdominal discomfort?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Bouts of abdominal pain?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Recurring bouts of feeling sick or vomiting?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Bouts of constipation (Normal=1 movement in 3 days to 3 in 1 day)	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Bouts of diarrhea?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Vomited blood?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Bleeding from the bowels?	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

84. (HAND CARD #84) Please look at this card and read the following, please tell me if you ever ' any of these conditions. READ a-g AND RECORD IN C N A OF CHART.

IF "NO" TO ALL...SKIP TO Q85
ALL OTHERS.....CONTINUE

B. In what year did (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or private doctor or hospital for the diagnosis and care o' the (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR OR HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

CONDITION	A. YES	A. NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS/CITY/STATE
a. Hepatitis with or without jaundice?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Cirrhosis of the liver?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Jaundice?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Gall bladder disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Gallstones?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Pancreatitis?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
g. Other diseases of the liver? (SPECIFY) ↳_____	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

85. Now some questions regarding renal conditions. By renal conditions we mean urinary, genital or kidney problems.

A. (HAND CARD #85) Please look at this card and as I read each, please tell me if you ever had any of the following. READ a-k AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q86 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Kidney or bladder stones?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Kidney infection?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Nephritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Renal colic?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Bladder infection?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Disorders of the prostate?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Urethritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
h. Gonorrhea?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
i. Syphilis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
j. Herpes?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
k. Other problems? SPECIFY: _____	1	2	19____	1	2	Military/Medical.....1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you currently seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF SEEING PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you are seeing for the (...) problem. RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS/CITY/STATE	F. CURRENT CARE	G. NAME/ADDRESS/CITY/STATE CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

86 Have you ever had an attack of painful or too frequent urination?

YES..... 1

NO.....SKIP TO Q87..... 2

A. When did this first occur?

RECORD YEAR:_____

B. Is it still a problem?

YES..... 1

NO..... 2

C. Have you seen a doctor about these symptoms?

YES..... 1

NO.....SKIP TO Q87..... 2

D Where did you receive your diagnosis and care for painful or too frequent urination? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

Do you have to get up more than once a night to pass urine?

YES..... 1

NO.....SKIP TO Q88..... 2

A. Is this a life-long habit?

YES.....SKIP TO Q88..... 1

NO..... 2

B. In what year did this habit change?

RECORD YEAR:_____

C. Have you seen a doctor about these symptoms?

YES..... 1

NO.....SKIP TO Q88..... 2

D. Where did you receive your diagnosis and care for nighttime urination? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

88. Have you ever passed blood in your urine?

YES..... 1

NO.....SKIP TO Q89..... 2

A. In what year did you first pass blood in your urine?

RECORD YEAR:_____

B. Do you still pass blood in your urine?

YES..... 1

NO..... 2

C. Have you seen a doctor about these symptoms?

YES..... 1

NO.....SKIP TO Q89..... 2

D. Where did you receive your diagnosis and care for blood in your urine? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

Now some questions regarding tumors and growths.

A. (HAND CARD #89) Please look at this card and as I read each, please tell me if you ever had any of the following. READ a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q90 ALL OTHERS.....CONTINUE

B. In what year was (...) diagnosed? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. ASK FOR ONLY a-d: What kind of a (...) was that? RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of the (...)? CODE IN COLUMN D OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. KIND	D. DIAGNOSIS AND CARE
a. A cancer?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
b. A tumor?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
c. A lump?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
d. A growth?	1	2	19____	_____	Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
e. A sarcoma (tumor of soft tissue)?	1	2	19____		Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
f. A tumor of the eye?	1	2	19____		Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2
g. A tumor of the testes?	1	2	19____		Mil/Medical...GO TO F...1 Doctor/Hosp...ASK E.....2

IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

F. Are you currently seeing a Military Medical Service or private doctor/hospital for care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF CURRENTLY SEEING A PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address city and state of the doctor/hospital you are currently seeing for the (...). INSERT CONDITION FOR (...). RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS/CITY/STATE	F. CURRENT CARE	G. NAME/ADDRESS/CITY/STATE CURRENT DOCTOR/HOSPITAL
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	

90. N[illegible] some questions regarding allergies.

A. (HAND CARD #90) Please look at this card and as I read the following, please tell me if you have ever had any of these problems. READ a-f AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q91 ALL OTHERS.....CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) condition first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or a private doctor/hospital for the diagnosis and care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for the (...)? INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

	A. EVER HAD YES	A. EVER HAD NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	C. CURRENT PROBLEM NO	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS/CITY/STATE
a. Hives?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Other skin rashes?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
c. Hayfever (Vasomotor rhinitis)?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Asthma?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Stomach upsets?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Other allergies? SPECIFY: _____	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

91. A(AND CARD #91-92) Please look at this card and(read the following, please tell me if you have(r had a diagnosis of any of these diseases? READ a(AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q92
ALL OTHERS.....CONTINUE

B. FOR ALL "YES" ASK: Did you see a Military Medical Service or a private doctor/hospital for the diagnosis and care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you went to for the (...) condition. RECORD NAME AND ADDRESS IN COLUMN C OF CHART.

D. Are you <u>currently</u> receiving treatment for (...) from a Military Medical Service or a private doctor/hospital? INSERT CONDITION FOR (...). RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you are currently seeing for the (...) condition. INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

CONDITION	A. EVER HAD YES	A. EVER HAD NO	B. DIAGNOSIS AND CARE	C. NAME/ADDRESS/CITY/STATE	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS/CITY/STATE
a. Lupus erythematosis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
b. Hashimoto's thyroiditis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
c. Rheumatoid arthritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
d. Vitiligo?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
e. Pernicious anemia?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK C	

f. Pre[illegible]e testicular failure?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
g. Addison's disease?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
h. Primary biliary cirrhosis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
i. Temporal arteritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
j. Idiopathic thrombocytopenic purpura?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
k. Ulcerative colitis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
l. Regional ileitis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
m. Hypoparathyroidism?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
n. Polymyositis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	

Q132 (cont.)

CONDITION	A. EVER HAD YES	NO	B. DIAGNOSIS AND CARE	C. NAME AND ADDRESS	D. DIAGNOSIS AND CARE	E. NAME AND ADDRESS
o. Polymyalgia rheumatica?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
p. Periarteritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
q. Dermatomyositis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
r. Scleroderma?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
s. Pemphigus?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
t. Urticaria?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
u. Sjogren's syndrome?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	

v. Myasthenia gravis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 GO TO NEXT Doctor/Hosp..2 ASK E	
w. Glomerulo-nephritis?	1	2	Mil/Medical..1 GO TO D Doctor/Hosp..2 ASK C		Mil/Medical..1 Doctor/Hosp..2 ASK E	

92. Please look at the card again (HAND CARD #91-92) and tell me if anyone in your family, children, parents, aunts, uncles, etc. have ever been diagnosed for these diseases? READ a-w AND RECORD IN COLUMN I OF CHART.

A. IF "YES", ASK FOR RELATIONSHIP TO RESPONDENT.

CONDITION	I. YES	NO	II. RELATIONSHIP TO RESPONDENT
a. Lupus erythematosis?	1	2	
b. Hashimoto's thyroiditis?	1	2	
c. Rheumatoid arthritis?	1	2	
d. Vitiligo?	1	2	
e. Pernicious anemia?	1	2	
f. Premature testicular failure?	1	2	
g. Addison's disease?	1	2	
h. Primary biliary cirrhosis?	1	2	
i. Temporal arteritis?	1	2	
j. Idiopathic thrombocytopenic purpura?	1	2	
k. Ulcerative colitis?	1	2	
l. Regional ileitis?	1	2	
m. Hypoparathyroidism?	1	2	
n. Polymyositis?	1	2	
o. Polymyalgia rheumatica?	1	2	
p. Periarteritis?	1	2	
q. Dermatomyositis?	1	2	
r. Scleroderma?	1	2	
s. Pemphigus?	1	2	
t. Urticaria?	1	2	
u. Sjogren's syndrome?	1	2	
v. Myasthenia gravis?	1	2	
w. Glomerulonephritis?	1	2	

93. I would like to ask you about some nervous system disorders.

A. (HAND CARD #93) Please look at this card and as I read the following, please tell me if you ever had any of these conditions. READ a-i AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q94 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Stroke?	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Encephalitis?	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Meningitis?	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Peripheral neuropathy (i.e. weakness, numbness, tingling of hands or feet)	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Epilepsy?	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Convulsions or seizures?	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Brain tumor?	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
h. Head injury? IF YES: Did you lose consciousness?	1 1	2 2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
i. Other (SPECIFY)? _____	1	2	19_____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you <u>currently</u> seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF SEEING PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you are seeing for the (...) problem. RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS/CITY/STATE	F. CURRENT CARE	G. NAME/ADDRESS/CITY/STATE CURRENT DOCTOR/HOSPITAL
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	

94. Have you ever had dizzy spells or blackouts (fits, faints or funny turns)?

YES..... 1
NO.....SKIP TO Q95..... 2

A. In what year did you first experience dizzy spells?

RECORD YEAR:_____

B. Do you still get dizzy spells, that is, in the last year?

YES..... 1
NO..... 2

C. How often did/do you have dizzy spells? Was/is it:

Once only,..... 1
Once a month or less often,..... 2
Several times a month,..... 3
Once a week,..... 4
Almost daily, or..... 5
Irregularly or in sprees?..... 6

D. Are/were the dizzy spells associated with:

	YES	NO
Headaches?.....	1	2
Nausea or vomiting?.....	1	2
Loss of balance?.....	1	2
Noise in the ears?.....	1	2
Difficulty with vision?.....	1	2
Certain head position?.....	1	2
Sense of spinning around?.....	1	2
Ear troubles?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1

NO.....SKIP TO Q95..... 2

F. Where did you receive your diagnosis and care for dizzy spells or blackouts? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

95. Have you ever had weakness or paralysis of any part of your body?

YES..... 1
NO.....SKIP TO Q96..... 2

A. Is/was the episode of weakness:

Short lived,..... 1
Recurrent or intermittent, or..... 2
Continuous?..... 3

B. How long did the episodes of weakness last? Would you say:

A few days at most,..... 1
1-3 months,..... 2
3-6 months,..... 3
6-12 months,..... 4
1-2 years, or..... 5
More than 2 years?..... 6

C. In what year did you first experience weakness in any part of your body?

RECORD YEAR:_____

D. Do you still experience this weakness, that is, in the last year?

YES..... 1
NO..... 2

E. Which part of your body is/was weak or lacking in power? Is/was it your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Leg or foot?.....	1	2
Both legs?.....	1	2
Hands and legs?.....	1	2
Both arms?.....	1	2
One side of the body?.....	1	2

F. Associated with the weakness, have you had:

	YES	NO
Double vision in one eye?.....	1	2
Double vision in both eyes?.....	1	2
Imbalance?.....	1	2
Dizziness?.....	1	2
Difficulty with speech?.....	1	2
Weakness in other parts of your body?.....	1	2
Blindness in one eye?.....	1	2
Dimming of vision in both eyes?.	1	2
Dimming of vision in one eye?...	1	2

G. Have you seen a doctor about these symptoms?

YES.....ASK H..... 1
NO.....SKIP TO Q96..... 2

H. Where did you receive your diagnosis and care for this weakness? Was it at:

A military medical service, or..... 1
A private doctor/hospital?..... 2
→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

6. Have you ever had numbness or loss of feeling of any part of your body?

YES..... 1
NO.....SKIP TO Q97..... 2

A. Was the numbness or loss of feeling associated with the weakness described previously?

YES.....SKIP TO Q97..... 1
NO..... 2

B. In what year did you first experience the numbness?

RECORD YEAR:_____

C. Do you still get numbness?

YES..... 1
NO..... 2

D. Which part of your body has/had been numb? Was it your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Leg or foot?.....	1	2
Both arms?.....	1	2
Both legs?.....	1	2
Hands and feet?.....	1	2
One side of the body?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q97..... 2

F. Where did you receive your diagnosis and care for your numbness? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

97. Have you ever suffered from persistent tingling or pins and needles?

YES..... 1
NO.....SKIP TO Q98..... 2

A. Has the tingling been associated with the weakness or numbness described previously?

YES..... 1
NO..... 2

B. In what year did you first experience tingling or pins and needles?

RECORD YEAR:_____

C. Do you still get tingling or pins and needles?

YES..... 1
NO..... 2

D. In which part of your body have you had pins and needles? Was it in your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Chest or abdomen?.....	1	2
Leg or foot?.....	1	2
Both arms?.....	1	2
Both legs?.....	1	2
Arms and legs?.....	1	2
One side of the body?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q98..... 2

F. Where did you receive your diagnosis and care for this tingling? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

8. Have you ever suffered from persistent or intermittent burning sensations in your muscles?

YES..... 1

NO.....SKIP TO G..... 2

A. Have these sensations been associated with weakness, numbness or tingling described previously?

YES.....SKIP TO Q99..... 1

NO..... 2

B. In what year did you first experience these sensations?

RECORD YEAR:_____

C. Are these sensations still a problem?

YES..... 1

NO..... 2

D. In which part of your body have you had these sensations? Was it your:

	YES	NO
Face?.....	1	2
Arm or hand?.....	1	2
Chest or abdomen?.....	1	2
Leg or foot?.....	1	2
Both arms?.....	1	2
Both legs?.....	1	2
One side of the body?.....	1	2

E. Have you seen a doctor about these symptoms?

YES.....ASK G..... 1

NO.....SKIP TO Q99..... 2

F. Where did you receive your diagnosis and care for these sensations? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

G. Have you ever had cramping in your calves?

YES..... 1

NO.....SKIP TO Q99..... 2

H. In what year did you <u>first</u> experience this cramping?

RECORD YEAR:_____

I. Have you seen a doctor about this cramping?

YES.....ASK J..... 1

NO.....SKIP TO Q99..... 2

J. Where did you receive your diagnosis and care for the cramping? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

99. Have you ever suffered from persistent involuntary movements or tremors?

YES..... 1
NO.....SKIP TO Q100..... 2

A. Were the tremors associated with weakness, numbness or tingling described previously?

YES.....SKIP TO Q100..... 1
NO..... 2

B. In what year did you first experience the tremors?

RECORD YEAR:_____

C. Do you still have trouble with tremors?

YES..... 1
NO..... 2

D. Where do you experience the tremors mainly? Is it in your:

Head,..... 1
Hands,..... 2
Legs, or..... 3
Over your whole body?..... 4

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q100..... 2

F. Where did you receive your diagnosis and care for these tremors? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

Have you had difficulty walking over a period of a month or more (excluding difficulty due to direct injury)?

YES..... 1
NO.....SKIP TO Q101..... 2

A. Do you still have any difficulty with walking?

YES..... 1
NO..... 2

B. In what year did you first experience difficulty walking?

RECORD YEAR:_____

C. Have you seen a doctor about these symptoms?

YES.....ASK D..... 1
NO.....SKIP TO Q101..... 2

D. Where did you receive your diagnosis and care for your difficulty walking? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

Q... This set of questions is about reproduction.

A. (HAND CARD #101) Please look at this card and as I read each condition, please tell me if you ever had any of the following. READ a-g AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q102 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Inflammation of the testes?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Tumor of the testes?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Hydrocele?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Varicocele?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Hernia?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Sterility?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Other problem? SPECIFY: _____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
_____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2

Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you currently seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF PRIVATE DOCTOR/HOSPITAL CURRENTLY SEEN, ASK: Please give me the name, address, city and state of the doctor/hospital you are currently seeing for the (...). RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS/CITY/STATE	F. CURRENT CARE	G. NAME/ADDRESS/CITY/STATE CURRENT DOCTOR/HOSPITAL
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2	
	Military/Medical.....1 Doctor/Hosp...ASK G...2 Military/Medical.....1 Doctor/Hosp...ASK G...2	

102 Have you ever had any venereal disease or V.D. such as: READ a-c AND CODE IN COLUMN I OF CHART.

	I. YES	I. NO	II. FIRST OCCURRED MONTH - YEAR	III. SERVING S. VIETNAM YES	III. SERVING S. VIETNAM NO	IV. MONTH - YEAR WHILE SERVING
a. Syphilis?	1	2	_____ 19____	1	2	_____ 19____
b. Gonorrhea?	1	2	_____ 19____	1	2	_____ 19____
c. Clap?	1	2	_____ 19____	1	2	_____ 19____

IF ALL "NO"...SKIP TO Q103
ALL OTHERS.....CONTINUE

A. What month and year did you first have (...)? INSERT DISEASE FOR (...) - RECORD IN COLUMN II OF CHART ABOVE.

B. Did you have (...) while serving in South Vietnam? ASK FOR EACH "YES" IN COLUMN I - INSERT DISEASE FOR (...) - CODE IN COLUMN III OF CHART ABOVE.

C. What month and year did you have (...) while serving in South Vietnam? INSERT DISEASE FOR (...) - RECORD MONTH AND YEAR IN COLUMN IV OF CHART ABOVE.

103. Have you ever had the mumps?

YES.....ASK A..... 1
NO.....SKIP TO Q104..... 2

A. When did you have the mumps?

RECORD YEAR:_____

B. When you had the mumps did you have any swelling of the testicles at that time?

YES..... 1
NO..... 2
DK/DR..... 9

94. I would like to ask you some questions about fertility, i.e. your ability to father children.

A. Have you fathered <u>any</u> children or been responsible for a pregnancy?

YES..... 1
NO..... 2

B. Are you able to have an erection and ejaculate?

YES..... 1
NO..... 2

C Do you have any reason to believe that you are <u>currently</u> unable to father children?

YES..... 1
NO.....SKIP TO G..... 2

D. Why do you believe you are currently unable to father children? Is it because:

	YES	NO
You have tried to have children without success?	1 ASK E	2
You have had a vasectomy?	1 SKIP TO H	2
You and your partner don't wish to have intercourse?	1 SKIP TO G	2
You have had a sperm count and it is low?	1 ASK G	2
Other reason? (SPECIFY) _____	1 SKIP TO G	2

E. For how long have you been trying to have children? Would you say:

Less than 6 months,..... 1
6 months to 1 year,..... 2
1 to 2 years, or..... 3
More than 2 years?..... 4

F When you were trying to make your partner pregnant how often would you have intercourse? Would you say:

Daily,..... 1
Several times a week,..... 2
Once a week,..... 3
Twice a month,..... 4
Once a month, or..... 5
Less than once a month?..... 6

G. Are you currently avoiding having children?

Yes..... 1
NO.....SKIP TO I..... 2

H. Why are you avoiding having children? Is it because you are:

Planning not to have a family,..... 1
Spacing family, or..... 2
Some other reason?..... 3
→SPECIFY:_____

I. Do you or your partner use contraception?

YES..... 1
NO.....SKIP TO K..... 2
NO PARTNER.....SKIP TO K..... 3
DON'T KNOW.....SKIP TO K..... 8

J. (HAND CARD #104J) Please look at this card and tell me what method of contraception you and your partner <u>usually</u> use?

CONDOM.....01
PILL.....02
IUD.....03
TEMPERATURE.....04
DIAPHRAGM.....05
TUBAL LIGATION.....06
VASECTOMY.....07
RHYTHM.....08
OTHER.....09
↳SPECIFY:_____

K. How would you rate your interest in sex at present? Would you say:

Increased interest for you,.....SKIP TO Q105..... 1
Normal for you, or..SKIP TO Q105..... 2
Decreased interest for you?.....ASK L..... 3

L. When did your interest <u>first</u> change?

RECORD YEAR:_____

105. How many children are you the natural father of? Please include children who were stillborn, who are no longer living, or who do not live with you. Do not include stepchildren, foster children or adopted children.

RECORD # OF CHILDREN:_____

NO CHILDREN.....SKIP TO Q107.....99

106. Have you fathered any children from your present wife or partner?

YES..... 1

NO.....SKIP TO Q107..... 2

NO PRESENT PARTNER..SKIP TO Q108..... 9

A. Now I would like to list all of your children from your present wife or partner. Please include children who do not live with you and children who are no longer living. Starting with your oldest child, please give me the first and last names of each live birth. Tell me if the child is a boy or girl, the child's date of birth and whether the child is living, or deceased. RECORD IN ROSTER - COLUMNS a-e.

CHILDREN FROM PRESENT WIFE(PARTNER)

a. GIVEN NAME	b. SURNAME	c. SEX M	F	DK	d. DATE OF BIRTH MONTH	YEAR	e. LIVING	DE-CEASED
1.		1	2	9	___	19___	1	2
2.		1	2	9	___	19___	1	2
3.		1	2	9	___	19___	1	2
4.		1	2	9	___	19___	1	2
5.		1	2	9	___	19___	1	2
6.		1	2	9	___	19___	1	2
7.		1	2	9	___	19___	1	2
8.		1	2	9	___	19___	1	2
9.		1	2	9	___	19___	1	2
10.		1	2	9	___	19___	1	2
11.		1	2	9	___	19___	1	2
12.		1	2	9	___	19___	1	2

B. Have you and your present wife or partner had any stillbirths?

YES.....ASK C..... 1

NO.....SKIP TO Q107..... 2

C. Now please tell me about any stillbirths from your present wife or partner. Please tell me if the child was a boy or girl and the date of birth.

STILLBIRTHS FROM PRESENT WIFE (PARTNER)

	SEX			DATE OF BIRTH	
	M	F	DK	MONTH	YEAR
1.				_____	19____
2.				_____	19____
3.				_____	19____
4.				_____	19____
5.				_____	19____
6.				_____	19____

D. Do you know of anyone in your or your present wife's/partner's family who has had any stillbirths?

YES..... 1

NO.....SKIP TO Q107..... 2

a. Whose family was that? Was it:

Your family, or..... 1

Your wife's/partner's?..... 2

BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO WIFE/PARTNER:

_____

107. Now I need to ask a few questions about your present wife/partner

A. How old is she?

RECORD AGE:_____

B. Please give me her date of birth?

RECORD:_____/_____
MONTH YEAR

C. What racial or ethnic group does she identify with?

RECORD:_____

D. How many years of school did she complete and receive credit for?

RECORD:_____

IF NO NATURAL CHILDREN SIRED (Q105)...SKIP TO Q112

108. Have you fathered <u>any</u> children from any <u>previous</u> wife or partner?

YES..... 1

NO.....SKIP TO INSTRUCTION BOX ABOVE Q109..... 2

A. Now I would like to list all of your children from your <u>previous</u> wife or partner. Please include children who do not live with you and children who are no longer living. Starting with your oldest child, please give me the first and last names of each live birth. Tell me if the child is a boy or girl, the child's date of birth and whether the child is living or deceased. RECORD IN ROSTER - COLUMNS a-e.

<u>CHILDREN FROM PREVIOUS PARTNER(S)</u>

a. GIVEN NAME	b. SURNAME	c. SEX M	F	DK	d. DATE OF BIRTH MONTH	YEAR	e. LIVING	DE-CEASED
1.		1	2	9	___	19___	1	2
2.		1	2	9	___	19___	1	2
3.		1	2	9	___	19___	1	2
4.		1	2	9	___	19___	1	2
5.		1	2	9	___	19___	1	2
6.		1	2	9	___	19___	1	2
7.		1	2	9	___	19___	1	2
8.		1	2	9	___	19___	1	2
9.		1	2	9	___	19___	1	2
10.		1	2	9	___	19___	1	2
11.		1	2	9	___	19___	1	2
12.		1	2	9	___	19___	1	2

B. Have you and your previous wife or partner had any stillbirths?

YES.....ASK C..... 1

NO.....SKIP TO Q109..... 2

C. Now please tell me about any stillbirths from your previous wife or partner. Please tell me if the child was a boy or girl and the date of birth.

STILLBIRTHS FROM PREVIOUS WIFE (PARTNER)

	SEX			DATE OF BIRTH	
	M	F	DK	MONTH	YEAR
1.				_____	19_____
2.				_____	19_____
3.				_____	19_____
4.				_____	19_____
5.				_____	19_____
6.				_____	19_____

D. Do you know of anyone in your or your <u>previous</u> wife's/partner's family who has had any stillbirths?

YES..... 1

NO.....SKIP TO Q109..... 2

a. Whose family was that? Was it:

Your family, or..... 1

Your wife's/partner's?..... 2

BOTH..... 3

b Who was that?

RELATIONSHIP TO RESPONDENT:

↳ _____

RELATIONSHIP TO WIFE/PARTNER:

↳ _____

REFER TO ROSTERS 106 AND 108:

IF NO CHILDREN.....SKIP TO INTRO Q112
IF ANY DECEASED OR STILLBORN CHILDREN...ASK Q109
ALL OTHER.....SKIP TO Q110

109. Could you tell me something about the child(ren) who is (are) no longer living? Please give me the child's name, date of death, place and cause of death, and the names and addresses of any doctors or hospitals who treated the child.

a. First name:_____

Date of death:_____

Place of death:_____

_____

Cause of death:_____

Doctor/hospital name:_____

_____

Address/City/State:_____

_____

b. First name:_____

Date of death:_____

Place of death:_____

_____

Cause of death:_____

Doctor/hospital name:_____

_____

Address/City/State:_____

_____

A. Could you tell me something about the stillbirth(s)? For example:

a. Date of birth:_____

Place of birth (name of hospital, city):

_____

Cause of stillbirth:_____

b. Date of birth:_____

Place of birth (name of hospital, city):

_____

Cause of stillbirth:_____

10. Were any of the children that you mentioned born with an abnormality or any physical or mental handicap, including those who are now dead or stillbirths?

YES..... 1
NO.....SKIP TO Q111..... 2
DON'T KNOW..... 9

A. How many?

RECORD #:_____

B. Please tell me the:

Given name of child:_____

Type of defect or handicap:_____

_____

a. Has/had the child received medical attention for this condition?

YES.....ASK b..... 1
NO.....SKIP TO NEXT CHILD OR E..... 2

b. Please give me the name of the doctor, hospital, or institution and the address.

_____

_____

_____

C. Given name of child:_____

Type of defect or handicap:_____

_____

a. Has/had the child received medical attention for this condition?

YES.....ASK b..... 1
NO.....SKIP TO NEXT CHILD OR E..... 2

b. Please give me the name of the doctor, hospital, or institution and the address.

_____

_____

_____

D. Given name of child: _____

Type of defect or handicap: _____

_____

a. Has/had the child received medical attention for this condition?

YES.....ASK b..... 1

NO.....SKIP TO E..... 2

b. Please give me the name of the doctor, hospital, or institution and the address.

_____

_____

_____

E. Has a close relative, either in <u>your family</u> or the <u>child's mother's family</u>, had a similar problem?

YES.....ASK a..... 1

NO.....SKIP TO Q111..... 2

DON'T KNOW.....SKIP TO Q111..... 9

a. Whose family was that? Was it:

Your family, or..... 1

The child's mother's family?..... 2

BOTH..... 3

b. Who was that?

┌RELATIONSHIP TO RESPONDENT:

└_____

┌RELATIONSHIP TO CHILD'S MOTHER:

└_____

11. Have any of the children you mentioned ever been diagnosed as having cancer, including leukemia or cancer of the blood?

YES..... 1

NO.....SKIP TO Q112..... 2

A. How many?

RECORD #:_____

a. Please give me the:

Given name of child:_____

Type and site of malignancy:_____

Year of diagnosis:_____

Name and address of doctor or hospital who diagnosed and/or treated the child:

_____

_____

_____

B. Has a close relative either in your family or the child's mother's family had a similar problem?

YES.....ASK B..... 1

NO.....SKIP TO Q112..... 2

DON'T KNOW.....SKIP TO Q112..... 9

C. Whose family was that? Was it:

Your family, or..... 1

The child's mother's family?..... 2

BOTH..... 3

D. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO CHILD'S MOTHER:

_____

12. Did any pregnancy in which you were the partner end in a miscarriage or abortion?

YES.....ASK A..... 1

NO.....SKIP TO Q113..... 2

DON'T KNOW.....SKIP TO Q113..... 9

A. How many such pregnancies were there?

RECORD #:_____

a. In which year did the pregnancy(s) end?

RECORD YEAR:_____

_____

b. Was there any reason to believe the child had any abnormalities or defects?

YES..... 1

NO..... 2

c. Please tell me the name and address of the hospital or doctor who treated her:

_____

_____

_____

d. Was the mother your present wife or partner?

YES.....SKIP TO f..... 1

NO.....ASK e..... 2

e. Could you tell me the name and current address of the mother?

_____

_____

_____

f. Do you know of anyone in <u>your</u> or the mother's family who has had pregnancies which ended in miscarriages or any other serious problems with the pregnancy?

YES..... 1

NO.....SKIP TO Q113..... 2

a. Whose family was that? Was it:

Your family, or..... 1
The mother's family?..... 2
BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:
_____

RELATIONSHIP TO MOTHER:
_____

IF MORE THAN ONE IN Q112A ASK g-1...ALL OTHERS SKIP TO Q113

g. In which year did the next pregnancy end?

RECORD YEAR:_____

h. Was there any reason to believe the child had any abnormalities or defects?

YES..... 1
NO..... 2

i. Please tell me the name and address of the hospital or doctor who treated her:

_____
_____
_____

j. Was the mother your present wife or partner?

YES.....SKIP TO 1..... 1
NO.....ASK k..... 2

k. Could you tell me the name and current address of the mother?

_____
_____
_____

1. Do you know of anyone in your or the mother's family who has had pregnancies which ended in miscarriages or any other serious problems with the pregnancy?

YES..... 1

NO.....SKIP TO Q113..... 2

a. Whose family was that? Was it:

Your family, or..... 1

The mother's family?..... 2

BOTH..... 3

b. Who was that?

RELATIONSHIP TO RESPONDENT:

_____

RELATIONSHIP TO MOTHER:

_____

w we have some questions about blood and glandular disorders.

113. Have you ever had a tendency to bleeding or bruising easily?

YES.....ASK A..... 1
NO.....SKIP TO Q114..... 2

A. In what year did this tendency first occur?

RECORD YEAR:_____

B. Is bleeding or bruising still a problem?

YES..... 1
NO..... 2

C. Is the tendency associated with any medications that you may have taken?

YES..... 1
NO..... 2

D. Do bleeding tendencies or blood disorders run in your family?

YES..... 1
NO..... 2

E. Have you seen a doctor about these symptoms?

YES.....ASK F..... 1
NO.....SKIP TO Q114..... 2

F. Where did you receive diagnosis and care for this bleeding and bruising problem? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

114. Have you ever suffered from a generalized gland enlargement?

YES.....ASK A..... 1
NO.....SKIP TO Q115..... 2

A. In what year did the gland enlargement first occur?

RECORD YEAR:_____

B. Are the enlarged glands still a problem?

YES..... 1
NO..... 2

C. Have you seen a doctor about these symptoms?

YES.....ASK D..... 1
NO.....SKIP TO Q115..... 2

D. Where did you receive diagnosis and care for the gland problem? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
→ SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

115. Have you had blood transfusions?

YES..... 1

NO.....SKIP TO Q116..... 2

A. Did a Military Medical Service or a private doctor/hospital administer the transfusion?

MILITARY MEDICAL SERVICE..... 1

DOCTOR/HOSPITAL..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

116. Now these are some questions about bones and joints.

A. (HAND CARD #116) Please look at this card and as I read each, please tell me if you ever had any of the following. READ a-l AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q117 ALL OTHERS.....CONTINUE

B. In what year did the (...) first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE
a. Osteoarthritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
b. Rheumatoid arthritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
c. Gout?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
d. Other arthritis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
e. Sciatica?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
f. Disc trouble?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
g. Spondylitis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
h. Lumbago?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
i. Systemic lupus erythematosis?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
j. Scleroderma?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
k. Pagets disease?	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2
l. Other (SPECIFY) _____	1	2	19____	1	2	Military/Medical...GO TO F...1 Doctor/Hospital....ASK E.....2

D. Did you see a Military Medical Service or private doctor/hospital for the diagnosis and care of (...)? RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for (...). INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E.

F. Are you currently seeing a Military Medical Service or a private doctor/hospital for the (...) problem? INSERT CONDITION FOR (...). RECORD IN COLUMN F OF CHART.

G. IF PRIVATE DOCTOR/HOSPITAL CURRENTLY SEEN, ASK: Please give me the name, address, city and state of the doctor/hospital you are currently seeing for the (...). RECORD IN COLUMN G OF CHART.

E. NAME/ADDRESS/CITY/STATE	F. CURRENT CARE	G. NAME/ADDRESS/CITY/STATE CURRENT DOCTOR/HOSPITAL
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	
	Military/Medical......1 Doctor/Hosp...ASK G...2	

7. Have you <u>ever</u> had an injury to a joint(s)?

YES..... 1
NO.....SKIP TO Q118..... 2

A. In what year did the <u>initial</u> injury occur?

RECORD YEAR:_____

B. Is the joint still a problem?

YES..... 1
NO..... 2

C. Have you seen a doctor about these symptoms?

YES.....ASK D..... 1
NO.....SKIP TO Q118..... 2

D. Where did you receive diagnosis and care for the injury to a joint(s)? Was it at:

A military medical service, or..... 1
A private doctor or hospital?..... 2
↳ SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

118. Apart from injury have you ever had hot painful, swollen or stiff joints?

YES..... 1
NO.....SKIP TO Q119..... 2

A. Which joints were affected?

ONE..... 1
SEVERAL SYMMETRICAL..... 2
SEVERAL ASYMMETRICAL..... 3

B. In what year did you <u>first</u> have painful or swollen joints?

RECORD YEAR:_____

C. Are these joints still a problem?

YES..... 1
NO..... 2

D. Have you seen a doctor about these symptoms?

YES.....ASK E..... 1
NO.....SKIP TO Q119..... 2

E. Where did you receive diagnosis and care for the painful or swollen joints? Was it at:

A military medical service, or..... 1
A private doctor/hospital?..... 2
→SPECIFY NAME, ADDRESS, CITY, STATE:

_____
_____
_____

119. The next list is about gland disorders.

A. (HAND CARD #119) Please look at this card and as I read the following, please tell me if you have ever had any of these problems. READ a-f AND RECORD IN COLUMN A OF CHART.

IF "NO" TO ALL...SKIP TO Q120 ALL OTHERS.....:CONTINUE

B. FOR EACH "YES" ASK: In what year did the (...) condition first occur? INSERT CONDITION FOR (...). RECORD IN COLUMN B OF CHART.

C. Is (...) still a problem? INSERT CONDITION FOR (...). RECORD IN COLUMN C OF CHART.

D. Did you see a Military Medical Service or a private doctor/hospital for the diagnosis and care of the (...)? INSERT CONDITION FOR (...). RECORD IN COLUMN D OF CHART.

E. IF PRIVATE DOCTOR/HOSPITAL, ASK: Please give me the name, address, city and state of the doctor/hospital you saw for the (...)? INSERT CONDITION FOR (...). RECORD NAME AND ADDRESS IN COLUMN E OF CHART.

CONDITION	A. EVER HAD YES	NO	B. YEAR OCCURRED	C. CURRENT PROBLEM YES	NO	D. DIAGNOSIS AND CARE	E. NAME/ADDRESS/CITY/STATE
a. Diabetes?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
b. Thyroid condition - Was that an: Overactive, or	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
Underactive?	1	2					
DON'T KNOW	1	2					
BOTH	1	2					
c. Pituitary gland disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
d. Adrenal gland disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
e. Parathyroid gland disorder?	1	2	19____	1	2	Mil/Medical..GO TO NEXT..1 Doctor/Hosp..ASK E.....2	
f. Other (SPECIFY) _____	1	2	19____	1	2	Mil/Medical.....1 Doctor/Hosp..ASK E.....2	

20. Were you ever under care for mental or emotional problems such as a nervous breakdown, exhaustion, and so forth?

YES.....ASK A..... 1

NO.....THANK AND END..... 2

A. Have you seen a doctor about this problem?

YES.....ASK B..... 1

NO.....THANK AND END..... 2

B. Where did you receive diagnosis and care about your mental and emotional problems? Was it at:

A military medical service, or..... 1

A private doctor or hospital?..... 2

→SPECIFY NAME, ADDRESS, CITY, STATE:

_____

_____

_____

That completes the study. Thank you for your time and cooperation.

SPOUSE QUESTIONNAIRE

SPOUSE

QUESTIONNAIRE FOR AGENT ORANGE

DATE OF INTERVIEW:_____

INTERVIEWER ID#:_____

PLACE OF EXAMINATION:_____

First, I would like to ask you a few general questions about you and your family. This information is important for statistical purposes, to see how people in this survey compare with the rest of the population.

1. What is your full name?

NAME:_____
FIRST MIDDLE LAST

2. What is your birthdate?

RECORD:_____
MONTH DAY YEAR

3. Where were you born?

RECORD:_____
CITY STATE

4. What was the highest grade in school you completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL: SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

5. With which of the following racial or ethnic backgrounds do you identify? Would you say:

Black,..... 1
Hispanic,..... 2
Asian, or..... 3
White?..... 4
OTHER..... 5
→ SPECIFY:_____

6. What language was spoken in your home when you were growing up (up to age 16)?

ENGLISH.....01
SPANISH.....02
GERMAN.....03
JAPANESE.....04
CHINESE.....05
OTHER.....96
→ SPECIFY:_____

7. What is your present marital status? Are you:

Married,..... 1
Divorced,..... 2
Separated,..... 3
Widowed, or..... 4
Have you never been married?..... 5

8. What is your social security number?

RECORD: ___ ___ ___/___ ___/___ ___ ___ ___

9. Please tell me the different cities you lived in for at least 2 months, starting with the place you were born.

PLACES RESIDED (CITY, STATE)	DATES OF RESIDENCE FROM	TO
1.		
2.		
3.		
4.		
5.		
6.		

10. Who was the head of the household when you were growing up?

RECORD HEAD: _____

11. What was his/her major occupation during most of your childhood? (BE SPECIFIC - GET DETAILS)

_____

_____

What was the highest grade in school he/she completed and received credit for? CIRCLE ONE

GRADE SCHOOL 1 2 3 4 5 6 7 8

HIGH SCHOOL 9 10 11 12

YEARS OF COLLEGE OR POST HIGH SCHOOL TRAINING 13 14 15 16

GRADUATE SCHOOL (POST COLLEGE EDUCATION):

SOME POST COLLEGE - 17
MASTERS - 18
DOCTORATE - 19

NONE - 00

DON'T KNOW - 98

13. The next part of this questionnaire concerns jobs that you have held.

I am interested in <u>all</u> the different kinds of work you have done for a period of <u>one month</u> or more. Please include summer jobs or part-time jobs you may have held while you were going to school.

First, are you <u>currently</u> employed, either full or part-time?

YES.....ASK A..... 1 →

NO.....ASK A..... 2 →

	13A. TITLE What is (was) your main title?	13B. DUTIES What are (were) your major duties on this job? PROBE.
CURRENT (MOST RECENT) JOB		

A. IF YES -- What is your present job title? ASK A-C. THEN SHOW CARD #13D. On this card is a list of exposures that might affect your health. Please tell me if you have been or are exposed to any harmful substance on your present job. RECORD IN COLUMN D. When did you start working at this job? RECORD IN COLUMN E.

IF NO -- What was your last job title? ASK A-C. THEN SHOW CARD #13D. On this card is a list of exposures that might affect your health. Please tell me if you were exposed to any harmful substance on your last job. RECORD IN COLUMN D. When did you start working at this job? RECORD IN COLUMN E. When was the ending date of your last job? RECORD IN COLUMN F.

What other types of jobs did you have since you were 16 years old, besides (your current/your most recent) job? RECORD ON CHART - ASK A-F.

13C. COMPANY What kind of company is (was) this? What type of industry was that in?	13D. EXPOSURES Which substances are (were) you exposed to?	13E. START DATE When did you start this job?		13F. END DATE When did this job end?	
		MONTH	YEAR	MONTH	YEAR

4. On this card (HAND CARD #14) is a list of exposures that might affect your health. Please tell me about these or other substances you think might have been harmful to which you may have been exposed either in a job, hobby, or any other situation. Please tell me if you have worked with or been exposed to any of these at least once a week for more than one month. Even though you may have mentioned them, please tell me again. RECORD IN CHART BELOW.

Exposure (RECORD SPECIFICS - FOR EXAMPLE: ON THE JOB, A HOBBY, ETC.)	When were you <u>first</u> exposed to this?		When was the last time you were exposed to this?	
	MONTH	YEAR	MONTH	YEAR

15. Other than the jobs you have just told me about, have you ever worked either for pay or not on a farm or other agricultural setting?

YES.....ASK A & B..... 1

NO.....SKIP TO Q16..... 2

A. When and where did you do this work?

B. What chemicals were you exposed to, chemicals such as insecticides, fungicides, herbicides, sprays or powders?

DATES	WHERE	CHEMICALS

16. Have you ever worked with or around anesthetic gases or radiation?

YES.....ASK A & B..... 1

NO.....SKIP TO Q17..... 2

A. When did you work with these?

B. Which anesthetic gases or radiation were you exposed to?

DATES	GASES/RADIATION

7. Have you ever smoked marijuana regularly for a period of at least one month?

YES..... 1

NO.....SKIP TO Q19..... 2

A. When did you start smoking marijuana on a fairly regular basis?

RECORD DATE: ____/____
MONTH YEAR

B. These days, do you smoke marijuana fairly regularly?

YES..... 1

NO..... 2

IF "YES" TO Q17B - ENTER [0|0] [0|0] IN BOX OF Q17C AND SKIP TO Q18

IF "NO" TO Q17B - ASK Q17C

C. When did you last smoke marijuana on a fairly regular basis?

RECORD DATE: [|] [|]
MO. YR.

18. You said that you (last smoked marijuana on a fairly regular basis in (END DATE)/are currently smoking marijuana on a fairly regular basis). HAND CARD #18 Please look at this card and tell me which category best describes how often you smoked marijuana during the last three months (that you smoked on a fairly regular basis)?

EVERY DAY..... 6
4 TO 6 DAYS A WEEK..... 5
2 OR 3 DAYS A WEEK..... 4
ONCE A WEEK..... 3
2 OR 3 DAYS A MONTH..... 2
ONCE A MONTH..... 1

A. HAND CARD #18A On the days that you smoked marijuana, about how many joints did you smoke per day?

LESS THAN ONE A DAY..... 1
1 OR 2 A DAY..... 2
3 OR 4 A DAY..... 3
5 OR 6 A DAY..... 4
7 OR 8 A DAY..... 5
9 OR 10 A DAY..... 6
MORE THAN 10 A DAY..... 7
→HOW MANY?_____

19. Have you <u>ever</u> used barbiturates <u>regularly</u> for a period of at least <u>one</u> month? You might know barbiturates as "barbs," "downers," Nembutol, Seconal, Amytol, Doriden, Quaalude, Methaqualone, "Sopors," Reds, Rainbows, or Yellow Jackets?

YES..... 1

NO.....SKIP TO Q20..... 2

A. When did you start using barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you <u>still</u> use barbiturates?

YES.....SKIP TO Q20..... 1

NO..... 2

C. When did you last use barbiturates?

RECORD: ☐☐ ☐☐
MO. YR.

20. Have you <u>ever</u> used amphetamines regularly for a period of at least <u>one</u> month? You might know amphetamines as "dexies," "uppers," "bennies," "diet pills," "speed," "crystals," methedrine, Benzadrine or Dexadrine.

YES..... 1

NO.....SKIP TO Q21..... 2

A. When did you start using amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you <u>still</u> use amphetamines?

YES.....SKIP TO Q21..... 1

NO..... 2

C. When did you <u>last</u> use amphetamines?

RECORD: ☐☐ ☐☐
MO. YR.

21. Have you ever used opiates regularly for a period of at least one month? You might know opiates as heroin, morphine, opium, codeine.

YES..... 1
NO.....SKIP TO Q22..... 2

A. When did you start using opiates?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use opiates?

YES.....SKIP TO Q22..... 1
NO..... 2

C. When did you last use opiates?

RECORD: ☐☐ ☐☐
MO. YR.

22. Have you ever used cocaine regularly for a period of at least one month?

YES..... 1
NO.....SKIP TO Q23..... 2

A. When did you start using cocaine?

RECORD: ☐☐ ☐☐
MO. YR.

B. Do you still use cocaine?

YES.....SKIP TO Q23..... 1
NO..... 2

C. When did you last use cocaine?

RECORD: ☐☐ ☐☐
MO. YR.

23. Have you ever used intravenous drugs, "shot up?"

YES.....ASK A..... 1

NO.....SKIP TO Q24..... 2

A. Which ones?

1._____

2._____

3._____

Next we have some questions about your health.

24. First, how tall are you?

RECORD: _____ / _____
FEET INCHES

25. What is your present weight?

RECORD: _____
LBS.

26. Have you ever had any endocrine or hormone problems such as diabetes or thyroid problems (too much or too little)?

YES.....ASK A-D..... 1

NO.....SKIP TO Q27..... 2

A. What is/was the problem(s)?

B. When did the problem first occur?

C. How was the (...) problem treated? (PROBE)

D. Do you still have the (...) problem?

ASK A-D FOR EACH PROBLEM MENTIONED AND RECORD IN APPROPRIATE COLUMN OF CHART.

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED	D. PROBLEM STILL PRESENT YES	NO
			1	2
			1	2
			1	2
			1	2

27. Do you have any chronic medical conditions? By that I mean something which keeps coming back or which requires constant medical treatment?

YES.....ASK A-C..... 1

NO.....SKIP TO Q28..... 2

A. What is/are the condition(s)?

B. When did (...) condition first occur?

C. How has (...) condition been treated? (PROBE)

ASK A-C FOR EACH CONDITION MENTIONED AND RECORD IN APPROPRIATE COLUMN OF CHART.

A. CONDITION	B. DATE FIRST OCCURRED	C. HOW TREATED

28. Now I would like to ask some questions about your reproductive system and any pregnancies you may have had.

At what age did your periods first start?

RECORD AGE:_____

29. Other than when you were pregnant, have there been times when you were not having periods or your periods were irregular?

YES.....ASK A-D..... 1

NO.....SKIP TO Q30..... 2

A. What was the problem(s)?

B. When did this first occur?

C How was it treated? (PROBE)

D. Is it still a problem?

ASK A-D FOR EACH PROBLEM MENTIONED
RECORD IN APPROPRIATE COLUMN OF CHART.

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED	D. PROBLEM STILL PRESENT	
			YES	NO
			1	2
			1	2
			1	2
			1	2

30. Have you ever had fibroids or any other problems with your uterus or womb?

YES.....ASK A-C..... 1
NO.....SKIP TO Q31..... 2

A. What was/were the problem(s)?

B. When did this occur?

C. How was it treated? (PROBE)

ASK A-C FOR EACH PROBLEM MENTIONED
RECORD IN CHART BELOW.

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED

31. Have you ever taken birth control pills?

YES..... 1
NO.....SKIP TO Q32..... 2

A. What dates did you take them?

START DATE	STOP DATE

32. Have you <u>ever</u> been hospitalized for any reason <u>other</u> than childbirth?

YES.....ASK A-C..... 1
NO.....SKIP TO Q33..... 2

A. Why were you hospitalized?
B. When were you hospitalized?
C. What treatment were you given? (PROBE)

ASK A-C FOR EACH HOSPITALIZATION MENTIONED
RECORD IN CHART BELOW.

A. PROBLEM	B. DATE	C. TREATMENT

33. How would you rate your health today? Would you say it is:

Excellent,..... 1
Good,..... 2
Fair, or..... 3
Poor?..... 4

34. Have you ever suffered from mental or emotional problems such as a nervous breakdown, exhaustion, and so forth?

YES.....ASK A-C..... 1

NO.....SKIP TO Q35..... 2

A. What was the problem?

B. When did this happen?

C. What kind of treatment did you receive?

ASK A-C FOR EACH PROBLEM MENTIONED.
RECORD IN CHART BELOW.

A. PROBLEM	B. DATE	C. TREATMENT

35. Have you ever felt you were under severe or unusual stress?

YES.....ASK A-C..... 1

NO.....SKIP TO Q36..... 2

A. What was the problem?

B. When did this happen?

C. What did you do about it?

ASK A-C FOR EACH MENTION.
RECORD IN CHART BELOW.

A. PROBLEM	B. DATE	C. WHAT YOU DID

36. Please look at this card (HAND CARD #36) and for each item tell me if you have ever had the problem, and if so, at what age it began and the nature of the problem. First:

	PROBLEM YES	PROBLEM NO	AGE AT ONSET	NATURE OF PROBLEM
Ulcers or other stomach or intestinal problems?	1	2		
Epilepsy or other nervous system disorders?	1	2		
Heart disease?	1	2		
Recurrent urinary system disorders (kidney or bladder trouble)?	1	2		
Chronic lung disease such as tuberculosis or emphysema?	1	2		
Venereal disease?	1	2		
Major nutritional disturbances?	1	2		
High blood pressure?	1	2		

37. Have you ever taken any of the following types of medications regularly and, if so, when?

	YES	NO	DATE
Thyroid medication?	1	2	
Steroids (cortisone)?	1	2	
Anti-arthritic or rheumatoid preparations?	1	2	
Anti-allergy preparations?	1	2	
Tranquilizers?	1	2	
Anti-depressants?	1	2	
Appetite depressants?	1	2	
Anti-convulsants?	1	2	
Anti-coagulants?	1	2	
Spermicides?	1	2	

38. Have you ever been pregnant?

YES.....SKIP TO Q40..... 1

NO..... 2

39. Was there ever a time when you were trying to become pregnant and could not do so?

YES.....SKIP TO Q42..... 1

NO.....SKIP TO INSTRUCTION ABOVE Q44..... 2

40. How many times have you been pregnant?

RECORD #:_____

41. Was there ever a period of time when you were trying to become pregnant, and either could not do so, or it took more than six months to do so?

YES..... 1

NO.....SKIP TO Q44..... 2

42. What is the most number of months or years at one stretch that you tried to become pregnant?

RECORD #:_____ MONTHS

_____ YEARS

43. Did your doctor feel that the delay in this pregnancy may have resulted from medical or other difficulties?

YES.....ASK A..... 1

NO.....SKIP TO INSTRUCTION BOX ABOVE Q44..... 2

A. What was the suspected cause for this delay of pregnancy?

_____

IF RESPONDENT NEVER PREGNANT...SKIP TO Q48

Next, I am going to ask you some questions about (each of your pregnancy(ies). I am interested in all of your pregnancies, even if they ended in a miscarriage or abortion.

A. When did your (first, second, etc.) pregnancy end? RECORD MONTH AND YEAR IN COLUMN A OF CHART.

B. What was the birth/due date for this infant? RECORD MONTH AND YEAR IN COLUMN B OF CHART.

C. How many months did this pregnancy last? RECORD NUMBER OF MONTHS IN COLUMN C OF CHART.

D. Did you have any problems during this pregnancy such as infection, unusual bleeding, swelling, high blood pressure, or vomiting? RECORD ANSWER IN COLUMN D OF CHART.

E. Did you have german measles during this pregnancy or were you exposed to a known case of german measles during this pregnancy? RECORD IN COLUMN E OF CHART.

Q40 # OF PREGS. _____

	A. MO/YR	B. BIRTH DUE DATE	C. # MOS.	D. PROBLEMS	E. HAVE MEASLES	F. MEDICATIONS/ DRUGS	G. WEIGHT (LBS.)
1st preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
2nd preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
3rd preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
4th preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
5th preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
6th preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
7th preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____
8th preg.	MO:____ YR:____	MO:____ YR:____	____	YES (SPECIFY).....1 →_____ NO.....2	YES...1 NO....2	YES (SPECIFY).....1 →_____ NO.....2	____

. were you taking any medications or drugs during this pregnancy? ... OF CHART.

. How much weight did you gain during this pregnancy? RECORD NUMBER OF POUNDS IN COLUMN G OF CHART.

. ... this pregnancy end with the birth of a live baby that lived at least one month? RECORD IN COLUMN H OF CHART.

Ha. How did it end? USE CODES IN BOX BELOW. IF ABORTION ASK Hb - ALL OTHERS GO TO NEXT PREGNANCY. RECORD IN COLUMN Ha OF CHART.

Hb. Was there any reason to think that the baby might have had a birth defect? RECORD IN COLUMN Hb OF CHART.

1. LB< 1 month	2. Stillborn	3. Miscarriage	4. Abortion	5. Ectopic

- CODES FOR COLUMN Ha

I. (ASK FOR EACH PREGNANCY) Please give me the name and address of the doctor/hospital involved with this pregnancy. RECORD NAME AND ADDRESS IN COLUMN I OF CHART.

H. LIVE BABY	Ha. HOW END	Hb. REASON FOR BIRTH DEFECT	I. DOCTOR/HOSPITAL NAME/ADDRESS
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
...GO TO NEXT.......1 ↳...E: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________
YES...GO TO NEXT.......1 ↳NAME: ________ NO....ASK Ha...........2	______	YES (SPECIFY).........1 ↳ ________ NO....................2	________ ________ ________

H. Did you breast feed this child? IF YES: When did you start and stop breast feeding? RECORD IN COLUMN H OF CHART.

I. Is this child alive at present? RECORD IN COLUMN I OF CHART.

J. Has/had this child had any serious illnesses such as cancer or leukemia? RECORD IN COLUMN J OF CHART. IF CHILD ALIVE - ASK ABOUT NEXT PREGNANCY OR Q46.

K. What was the date of the child's death? RECORD MONTH AND YEAR IN COLUMN K OF CHART.

L. What was the cause of death? RECORD IN COLUMN L OF CHART.

M. (ASK FOR EACH CHILD NO LONGER LIVING) Please give me the name and address of the doctor/hospital who cared for the child at the time of his/her death? RECORD IN COLUMN M OF CHART.

H. BREASTFEED (DATES)	I. ALIVE	J. ILLNESSES	K. DATE OF DEATH	L. CAUSE OF DEATH	M. DOCTOR/HOSPITAL NAME/ADDRESS
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO NEXT PREG OR Q46..2	MO____ YR____		
YES (SPEC)....1 ___/___ NO............2	YES...........1 NO............2	YES (SPEC)....1 ______ NO..GO TO Q46.......2	MO____ YR____		

REFER TO Q44Ha

IF PREGNANCY ENDED IN STILLBORN...ASK Q46......	1
ALL OTHERS.......................SKIP TO Q47..	2

46. Now, thinking of the pregnancies that ended in a stillbirth.

A. Was this a girl or boy? RECORD IN COLUMN A OF CHART.

B. How much did he/she weigh at birth? RECORD WEIGHT IN COLUMN B OF CHART.

C. What was his/her length at birth? RECORD IN COLUMN C OF CHART.

D. Were there any congenital abnormalities or birth defects in the baby? RECORD IN COLUMN D OF CHART.

Q44Ha
OF STILL-BORN ____

E Did this child have difficulty at the time of delivery? RECORD IN COLUMN E OF CHART.

F. Please give me the name and address of the doctor involved with this pregnancy? RECORD NAME AND ADDRESS IN COLUMN F OF CHART.

A. GIRL/ BOY	B. WEIGHT	C. LENGTH	D. ABNORMALITIES OR DEFECTS	E. DIFFICULT DELIVERY	F. DOCTOR NAME AND ADDRESS
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	
GIRL...1 BOY....2	LB____ OZ____	IN____	YES (SPECIFY)...1 →____________ NO.............2	YES (SPECIFY)....1 →____________ NO..............2	

47. Thinking about each of your pregnancy(ies) again, live births, stillbirths, miscarriages or abortions, please tell me:

A. If you ever smoked cigarettes during your (first, second, etc.) pregnancy? ASK FOR EACH PREGNANCY - CODE IN COLUMN A OF CHART.

B. What was the average number of cigarettes you smoked each day during your (first, second, etc.) pregnancy? RECORD NUMBER IN COLUMN B.

C. During your (first, second, etc.) pregnancy did you ever drink alcoholic beverages, such as beer, wine or hard liquor? RECORD IN COLUMN C.

D. During your (first, second, etc.) pregnancy how often did you drink alcohol? Would you say: RECORD IN COLUMN D.

Q40 # OF PREGS	A. EVER SMOKED	B. NUMBER OF CIGARETTES SMOKED EACH DAY	C. EVER DRINK ALCOHOL	D. HOW OFTEN DRANK
FIRST PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month,.....5 Once a month?.....6
SECOND PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month,.....5 Once a month?.....6
THIRD PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month,.....5 Once a month?.....6
FOURTH PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month,.....5 Once a month?.....6
FIFTH PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month,.....5 Once a month?.....6
SIXTH PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month,.....5 Once a month?.....6
SEVENTH PREGNANCY	YES..ASK B.....1 NO...SKIP TO C...2	_____	YES..ASK D.....1 NO...SKIP TO F...2	Daily.....1 4 to 6 days a week.....2 2 to 3 days a week.....3 Once a week.....4 2 or 3 days a month.....5

E. Which did you drink most during your (first, second, etc.) pregnancy, beer, wine, or hard liquor? RECORD IN COLUMN E.

F. On the days that you drank during your (first, second, etc.) pregnancy, about how many drinks did you have per day? RECORD IN COLUMN F.

G. During your (first, second, etc.) pregnancy did you ever use or take any drugs or narcotics? RECORD IN COLUMN G.

E. DRANK MOST	F. NUMBER OF DRINKS PER DAY	G. EVER TAKE DRUGS/NARCOTICS
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2
BEER...........1 WINE...........2 HARD LIQUOR....3	____________	YES...............1 NO................2

IF YES TO Q44Hb OR Q45E.....ASK Q48
IF NONE.....SKIP TO Q49

48. I notice that you had _____ baby(ies) with congenital abnormalities or birth defects. Do you know of anyone in your or the father's family who has had a similar problem?

YES.....ASK A..... 1
NO.....SKIP TO Q49..... 2

A. Who was that?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

49. Do you know of anyone in your or the father's family who has had miscarriages or stillbirths, or any other serious problems with a pregnancy?

YES.....ASK A..... 1
NO.....SKIP TO Q50..... 2

A. Who was that?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

50. Do you know of anyone in your or the father's family who has had a child with serious childhood illness, mental retardation, developmental problems or the like?

YES.....ASK A..... 1

NO.....SKIP TO Q51..... 2

A. Who was that and what was the problem?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

51. Were any of the pregnancies you have mentioned conceived while your husband was on leave from South Vietnam?

YES.....ASK A..... 1

NO.....SKIP TO Q52..... 2

A. Which one?

RECORD PREGNANCY #:_____

IF R IS NOT CURRENTLY MARRIED TO SAMPLED VETERAN...ASK Q'S 58 & 59

IF R IS CURRENTLY MARRIED TO SAMPLED VETERAN...CONTINUE WITH Q52

The last few questions are about your husband's or partner's health and will be useful in helping us to get a clear picture of his health generally.

52. Compared to other men his age, how would you rate the health of your husband or partner over the past 5 years? Would you say:

Very good,..... 1

Good,..... 2

Fair,..... 3

Poor, or..... 4

Very poor?..... 5

53. Has there been a major change in the health of your husband or partner over the past 10-15 years?

YES.....ASK A..... 1

NO.....SKIP TO Q54..... 2

A. Could you describe this change and give reasons why you think this change has occurred?

_____

_____

_____

_____

54. Compared to other men his age, how much of the time has your husband or partner been happy over the past 5 years? Would you say:

All of the time,..... 1

Most of the time,..... 2

Some of the time,..... 3

A little of the time, or..... 4

None of the time?..... 5

55. Has there been a major change in the behavior of your husband or partner over the past 10-15 years?

YES.....ASK A..... 1

NO.....SKIP TO Q56..... 2

A. Could you describe this change and give reasons why you think this change has occurred?

_____

_____

_____

_____

_____

56. Does the present behavior of your husband or partner prevent a normal family life?

YES.....ASK A..... 1

NO.....SKIP TO Q57..... 2

A. In what way does the present behavior of your husband or partner prevent a normal family life?

_____

_____

_____

_____

57. Would you please tell me anything else about your husband's or partner's health and/or behavior we have not mentioned and which you think may be of significance?

_____

_____

_____

_____

58. Please look at this card (HAND CARD #58) and give me the letter that comes closest to your total family income last year before taxes. Please include all sources, for example, wages, dividends, rentals, welfare, disability, etc.

A.	LESS THAN $3,000.....01	I.	$12,000 - $13,999.....09
B.	$3,000 - $3,999.....02	J.	$14,000 - $16,999.....10
C.	$4,000 - $4,999.....03	K.	$17,000 - $19,999.....11
D.	$5,000 - $5,999.....04	L.	$20,000 - $24,999.....12
E.	$6,000 - $6,999.....05	M.	$25,000 - $29,999.....13
F.	$7,000 - $8,499.....06	N.	$30,000 - $39,999.....14
G.	$8,500 - $9,999.....07	O.	$40,000 - $49,999.....15
H.	$10,000 - $11,999.....08	P.	$50,000 AND OVER.....16

REFUSED.....97

DON'T KNOW.....98

59. Do you own or rent your home (apartment)?

OWN..... 1

RENT..... 2

SOMETHING ELSE..... 3

→ SPECIFY:_____

60. We want to thank you for all the time you have given us. Your cooperation in this important study is vital to the success of the project. To complete our objectives in documenting your health status and health history we would like to contact the various hospitals, doctors or health care services you have mentioned in this interview so that we can look at your medical records. In order for us to do so, we need a signed release from you indicating your willingness to allow your medical records be made available to us. All information we collect will be kept strictly confidential and will be used for statistical and research purposes only. Your name or any details of your medical history will not be revealed. Are you willing to sign such a release?

YES.....GIVE CONSENT FORM

NO.....THANK AND TERMINATE

CONSENT FOR RELEASE OF MEDICAL RECORD INFORMATION

I hereby authorize the release of any medical records and information regarding my diagnosis and treatment to the investigators for the "Agent Orange Study."

_____ _____

SIGNATURE DATE

SOCIAL SECURITY # _____ _____ _____

INTERVIEWER SIGNATURE_____

DATE:_____

Do you have any chronic medical conditions? By that I mean something which keeps coming back or which requires constant medical treatment?

YES.....ASK A-C..... 1

NO.....SKIP TO Q54..... 2

A. What is/are the condition(s)/

B. When did (...) condition first occur?

C. How has (...) condition been treated? (PROBE)

ASK A-C FOR EACH CONDITION MENTIONED AND RECORD IN APPROPRIATE COLUMN OF CHART.

A. CONDITION	B. DATE FIRST OCCURRED	C. HOW TREATED

54. Now I would like to ask some questions about your reproductive system and any pregnancies you may have had.

At what age did your period first start?

RECORD AGE:_____

5. Other than when you were pregnant, have there been times when you were not having periods or your periods were irregular?

YES.....ASK A-D..... 1

NO.....SKIP TO Q56..... 2

A. What was the problem?

B. When did this first occur?

C. How was it treated? (PROBE)

D. Is it still a problem?

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED	D. PROBLEM STILL PRESENT	
			YES	NO
			1	2
			1	2
			1	2
			1	2

Have you ever had fibroids or any other problems with your uterus or womb?

YES.....ASK A-C..... 1
NO.....SKIP TO Q57..... 2

A. What was the problem?
B. When did this occur?
C. How was it treated? (PROBE)

A. PROBLEM	B. DATE FIRST OCCURRED	C. HOW TREATED

57. Have you ever taken birth control pills?

YES..... 1
NO.....SKIP TO Q58..... 2

A. What dates did you take them?

START DATE	STOP DATE

58. Have you ever been hospitalized for any reason other than childbirth?

YES.....ASK A-C..... 1
NO.....SKIP TO Q59..... 2

A. Why were you hospitalized?
B. When were you hospitalized?
C. What treatement were you given? (PROBE)

A. PROBLEM	B. DATE	C. TREATMENT

59. How would you rate your health today? Would you say it is:

Excellent,..... 1
Good,..... 2
Fair, or..... 3
Poor?..... 4

). Have you ever suffered from mental or emotional problems such as a nervous breakdown, exhaustion, and so forth?

YES.....ASK A-C..... 1

NO.....SKIP TO Q61..... 2

A. What was the problem?

B. When did this happen?

C. What kind of treatment did you receive?

A. PROBLEM	B. DATE	C. TREATMENT

1. Have you ever felt you were under severe or unusual stress?

YES.....ASK A-C..... 1

NO.....SKIP TO Q62..... 2

A. What was the problem?

B. When did this happen?

C. What did you do about it?

A. PROBLEM	B. DATE	C. WHAT YOU DID

. Please look at this card (HAND CARD #62) and for each item tell me if you have ever had the problem, and if so, at what age it began and the nature of the problem. First:

	PROBLEM YES	PROBLEM NO	AGE AT ONSET	NATURE OF PROBLEM
Ulcers or other stomach or intestinal problems?	1	2		
Epilepsy or other nervous system disorders?	1	2		
Heart disease?	1	2		
Recurrent urinary system disorders (kidney or bladder trouble)?	1	2		
Chronic lung disease such as tuberculosis or emphysema?	1	2		
Venereal disease?	1	2		
Major nutritional disturbances?	1	2		
High blood pressure?	1	2		

63. Have you ever taken any of the following types of medications regularly and, if so, when?

	YES	NO	DATE
Thyroid medication?	1	2	
Steroids (cortisone)?	1	2	
Anti-arthritic or rheumatoid preparations?	1	2	
Anti-allergy preparations?	1	2	
Tranquilizers?	1	2	
Anti-depressants?	1	2	
Appetite depressants?	1	2	
Anti-convulsants?	1	2	

64. Have you ever been pregnant?

YES.....SKIP TO Q66..... 1

NO..... 2

65. Was there ever a time when you were trying to become pregnant and could not do so?

YES.....SKIP TO Q68..... 1

NO.....SKIP TO INSTRUCTION ABOVE Q70..... 2

66. How many times have you been pregnant?

RECORD #:_____

7. Was there ever a period of time when you were trying to become pregnant, and either could not do so, or it took more than six months to do so?

YES..... 1

NO.....SKIP TO Q70..... 2

68. What is the most number of months or years at one stretch that you tried to become pregnant?

RECORD #:_____ MONTHS

_____ YEARS

69. Did your doctor feel that the delay in this pregnancy may have resulted from medical or other difficulties?

YES.....ASK A..... 1

NO.....SKIP TO INSTRUCTION BOX ABOVE Q70..... 2

A. What was the suspected cause for this delay of pregnancy?

_____

IF RESPONDENT NEVER PREGNANT.....SKIP TO Q73 192b

70. Next, I am going to ask you some questions about (each of your pregnancy(ies). I am interested in all of your pregnancies, even if they ended in a miscarriage or abortion.

A. When did your (first, second, etc.) pregnancy end? RECORD MONTH AND YEAR IN COLUMN A OF CHART.

B. What was the birth/due date for this infant? RECORD MONTH AND YEAR IN COLUMN B OF CHART.

C. How many months did this pregnancy last? RECORD NUMBER OF MONTHS IN COLUMN C OF CHART.

D. Did you have any problems during this pregnancy such as infection, unusual bleeding, swelling, high blood pressure, or vomiting? RECORD ANSWER IN COLUMN D OF CHART.

Q66 # OF PREGS. _____

	A. MO/YR	B. BIRTH/ DUE DATE	C. # MONTHS	D. PROBLEMS	E. HAVE MEASLES
First pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Second pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Third pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Fourth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Fifth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Sixth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Seventh pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2
Eighth pregnancy	MO:_____ YR:_____	MO:_____ YR:_____	_____	YES (SPECIFY).....1 ↳_____ NO.....2	YES.....1 NO.....2

E. Did you have german measles during this pregnancy or were you exposed to a known case of german measles during this pregnancy? RECORD IN COLUMN E OF CHART. 193b

F. Were you taking any medications or drugs during this pregnancy? RECORD IN COLUMN F OF CHART.

How much weight did you gain during this pregnancy? RECORD NUMBER OF POUNDS IN COLUMN G OF CHART.

H. Did this pregnancy end with the birth of a live baby that lived at least one month? RECORD IN COLUMN H OF CHART.

Ha. How did it end? USE CODES IN BOX BELOW. IF ABORTION ASK Hb - ALL OTHERS GO TO NEXT PREGNANCY. RECORD IN COLUMN Ha OF CHART.

Hb. Was there any reason to think that the baby might have had a birth defect? RECORD IN COLUMN Hb OF CHART.

1. LB< 1 month	2. Stillborn	4. Abortion
	3. Miscarriage	5. Ectopic

- CODES FOR COLUMN Ha

F. MEDICATIONS/DRUGS	G. WEIGHT (LBS)	H. LIVE BABY	Ha. HOW END	Hb. REASON FOR BIRTH DEFECT
YES (SPECIFY)...........1 → ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO....ASK Ha..........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 → ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 → ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 → ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 → ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 → ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO...ASK Ha...........2	______	YES (SPECIFY)......1 → ______ NO................2
YES (SPECIFY)...........1 ______ NO.....................2	______	YES...GO TO NEXT......1 →NAME: ______ NO....ASK Ha..........2	______	YES (SPECIFY)......1 → ______ NO................2

71. A. Did you have any problems with your labor or delivery with your (...) pregnancy? DO NOT ASK FOR PREGNANCIES NOT ENDING IN LIVE BIRTH. INSERT FIRST, SECOND, ETC. FOR (...). RECORD IN COLUMN A OF CHART.

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B. Was this a girl or boy? RECORD IN COLUMN B OF CHART.

C. How much did he/she weigh at birth? RECORD WEIGHT IN COLUMN C OF CHART.

D. What was his/her length at birth? RECORD LENGTH IN INCHES IN COLUMN D OF CHART.

E. Were there any congenital abnormalities or birth defects in the baby? RECORD IN COLUMN E OF CHART.

F. Did this child have difficulty at the time of delivery? RECORD IN COLUMN F OF CHART.

G. Did the child stay in the nursery after your discharge from the hospital? RECORD IN COLUMN G OF CHART.

A. PROBLEMS	B. GIRL/ BOY	C.	D. LENGTH	E. ABNORMALITIES OR DEFECTS	F. DIFFICULT DELIVERY	G. NURSERY
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2
YES (SPECIFY)....1 → ______ NO..............2	GIRL...1 BOY....2	LB_____ OZ_____	IN_____	YES (SPECIFY)..1 → ______ NO.............2	YES (SPECIFY)..1 → ______ NO.............2	YES...1 NO....2

H. Did you breast feed this child? IF YES: When did you start and stop breast feeding? RECORD IN COLUMN H OF CHART.

I. Is this child alive at present? RECORD IN COLUMN I OF CHART.

J. Has this child had any serious illnesses such as cancer or leukemia? RECORD IN COLUMN J OF CHART.

K. What was the date of the child's death? RECORD MONTH AND YEAR IN COLUMN K OF CHART.

L. What was the cause of death? RECORD IN COLUMN L OF CHART.

M. FOR DEATH, BIRTH DEFECT, STILLBORN, MISCARRIAGE, OR ABORTION WITH A SUSPECTED BIRTH DEFECT, ASK: Please give me the name and address of the doctor involved with this pregnancy? REFER TO Q70Ha & b, Q71E, Q71L. RECORD IN COLUMN M OF CHART.

H. BREASTFEED (DATES)	I. ALIVE	J. ILLNESSES	K. DATE OF DEATH	L. CAUSE OF DEATH	M. DOCTOR'S NAME/ADDRESS
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
(SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
YES (SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO NEXT PREG OR Q72..2	MO______ YR______		
(SPEC)....1 ____/____ NO............2	YES..GO TO K..1 NO...ASK J....2	YES (SPEC)....1 ____________ NO..GO TO Q72.......2	MO______ YR______		

IF YES TO Q70Hb OR Q71E.....ASK Q72
IF NONE.....SKIP TO Q73

72. I notice that you had _____ baby(ies) with congenital abnormalities or birth defects. Do you know of anyone in your or the father's family who has had a similar problem?

YES.....ASK A..... 1
NO.....SKIP TO Q73..... 2

A. Who was that?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

73. Do you know of anyone in your or the father's family who has had miscarriages or stillbirths, or any other serious problems with a pregnancy?

YES.....ASK A..... 1
NO.....SKIP TO Q74..... 2

A. Who was that?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

74. Do you know of anyone in your or the father's family who has had a child with serious childhood illness, mental retardation, developmental problems or the like?

YES.....ASK A..... 1
NO.....SKIP TO Q75..... 2

A. Who was that and what was the problem?

FATHER RELATIONSHIP	MOTHER RELATIONSHIP
_____	_____
_____	_____
_____	_____
_____	_____

75. Were any of the pregnancies you have mentioned conceived while your husband was on leave from South Vietnam?

YES.....ASK A..... 1
NO.....SKIP TO Q76..... 2

A. Which one?

RECORD PREGNANCY #:_____

The last few questions are about your husband's or partner's health and will be useful in helping us to get a clear picture of his health generally.

76. Compared to other men his age, how would you rate the health of your husband or partner over the past 5 years? Would you say:

Very good,..... 1
Good,..... 2
Fair,..... 3
Poor, or..... 4
Very poor?..... 5

77. Has there been a major change in the health of your husband or partner over the past 10-15 years?

YES.....ASK A..... 1
NO.....SKIP TO Q78..... 2

A. Could you describe this change and give reasons why you think this change has occurred?

78. Compared to other men his age, how much of the time has your husband or partner been happy over the past 5 years? Would you say:

All of the time,..... 1
Most of the time,..... 2
Some of the time,..... 3
A little of the time, or..... 4
None of the time?..... 5

79. Has there been a major change in the behavior of your husband or partner over the past 10-15 years?

YES.....ASK A..... 1
NO.....SKIP TO Q80..... 2

A. Could you describe this change and give reasons why you think this change has occurred?

80. Does the present behavior of your hsuband or partner prevent a normal family life?

YES.....ASK A..... 1

NO.....SKIP TO Q81..... 2

A. In what way does the present behavior of your husband or partner prevent a normal family life?

_____

_____

_____

_____

81. Would you please tell me anything else about your husband's or partner's health and/or behavior we have not mentioned and which you think may be of significance?

_____

_____

_____

_____

IF R IS NOT CURRENTLY MARRIED TO SAMPLED VETERAN...ASK Q'S 82 & 83

IF R IS CURRENTLY MARRIED TO SAMPLED VETERAN...THANK AND TERMINATE

82. Please look at this card (HAND CARD #82) and give me the letter that comes closest to your total family income last year before taxes. Please include all sources, for example, wages, dividends, rentals, welfare, disability, etc.

A.	LESS THAN $3,000.....01	I.	$12,000 - $13,999.....09
B.	$3,000 - $3,999.....02	J.	$14,000 - $16,999.....10
C.	$4,000 - $4,999.....03	K.	$17,000 - $19,999.....11
D.	$5,000 - $5,999.....04	L.	$20,000 - $24,999.....12
E.	$6,000 - $6,999.....05	M.	$25,000 - $29,999.....13
F.	$7,000 - $8,499.....06	N.	$30,000 - $39,999.....14
G.	$8,500 - $9,999.....07	O.	$40,000 - $49,999.....15
H.	$10,000 - $11,999.....08	P.	$50,000 AND OVER.....16

REFUSED.....97
DON'T KNOW.....98

83. Do you own or rent your home (apartment)?

OWN..... 1
RENT..... 2
SOMETHING ELSE..... 3
→ SPECIFY:_____

SPOUSE QUESTIONNAIRE HAND CARDS

CARD #17

A. CHEMICALS, CLEANING FLUIDS OR SOLVENTS (SPECIFY)

B. ASBESTOS, INSULATION MATERIAL

C. INSECTICIDES

D. PLASTICS OR RESINS (SPECIFY)

E. X-RAYS

F. ANESTHETIC GASES

G. RADIOACTIVITY, ISOTOPES

H. PETROLEUM PRODUCTS, FUELS BENZENE (SPECIFY)

I. LEAD OR METAL SMELTING FUMES (SPECIFY)

J. HERBICIDES (PLANT KILLERS)

CARD #45

EVERY DAY

4 TO 6 DAYS A WEEK

2 OR 3 DAYS A WEEK

ONCE A WEEK

2 OR 3 DAYS A MONTH

ONCE A MONTH

CARD #45A

LESS THAN ONE A DAY

1 OR 2 A DAY

3 OR 4 A DAY

5 OR 6 A DAY

7 OR 8 A DAY

9 OR 10 A DAY

MORE THAN 10 A DAY

CARD #62

ULCERS OR OTHER STOMACH OR INTESTINAL PROBLEMS

EPILEPSY OR OTHER NERVOUS SYSTEM DISORDERS

HEART DISEASE

RECURRENT URINARY SYSTEM DISORDERS (KIDNEY OR BLADDER TROUBLE)

CHRONIC LUNG DISEASE SUCH AS TUBERCULOSIS OR EMPHYSEMA

VENERAL DISEASE

MAJOR NUTRITIONAL DISTURBANCES

HIGH BLOOD PRESSURE

CARD #82

A. LESS THAN $3,000.....01

B. $3,000 - $3,999.....02

C. $4,000 - $4,999.....03

D. $5,000 - $5,999.....04

E. $6,000 - $6,999.....05

F. $7,000 - $8,499.....06

G. $8,500 - $9,999.....07

H. $10,000 - $11,999.....08

I. $12,000 - $13,999.....09

J. $14,000 - $16,999.....10

K. $17,000 - $19,999.....11

L. $20,000 - $24,999.....12

M. $25,000 - $29,999.....13

N. $30,000 - $39,999.....14

O. $40,000 - $49,999.....15

P. $50,000 AND OVER.....16

Table 1. Estimated quantities of herbicides and TCDD disseminated in South Vietnam from January 1962 - February 1971. (Reproduced from: Young, et al., 1978.)

Chemical	Pounds
2,4,5-D[a]	55,940,150
2,4,5-T[b]	44,232,600
TCDD[c]	368
Picloram[d]	3,041,800
Cacodylic Acid[e]	3,548,710
Total of Herbicides	106,763,260

[a] 2,4-D was an active ingredient in Herbicides Orange, Purple and White. From data in Table 7, the acid equivalents for 2,4-D in Herbicide Orange and White were calculated to be 4.14 lb/gal and 2.00 lb/gal, respectively. The acid equivalent for 2,4-D in Herbicde Purple was assumed to be 4.14 lb/gal.

[b] 2,4,5-T was an active ingredient in Green, Pink, Purple and Orange. Approximately 276,000 gal of Green, Pink and Purple were sprayed in South Vietnam prior to 1965, when it was replaced by Herbicide Orange. Herbicides Green and Pink contained 8.16 lb/gal 2,4,5-T. Herbicides Purple and Orange contained 4.00 lb/gal 2,4,5-T (Table 7).

[c] The mean TCDD concentration in Herbicde Purple was estimated at 32.8 ppm. The mean TCDD concentration in Herbicides Pink and Green was estimated at 65.6 ppm. The mean TCDD concentration in Herbicide Orange was estimated at 1.98 ppm.

[d] Picloram was an active ingredient of Herbicide White.

[e] Cacodylic acid was the active ingredient of Herbicide Blue. The Herbicide Blue formulation contained 15.4 percent arsenic in the pentavalent organic form. The value includes 10,000 lb cacodylic acid disseminated in South Vietnam from 1962-1964.

Table 2. Herbicides Used in Vietnam 1965-1971. (Reproduced from: National Academy of Science, 1974.)

Agent	Active Chemical Components	Military Application Rate (lb/acre)	Millions of gallons used, Aug. 1965-1971
Orange	2,4-D	12.00	
	2,4,5-T	13.80	11.22
White	2,4-D	6.00	
	Picloram	1.62	5.24
Blue	Cacodylic acid	9.30	1.12
Total			17.58

Appendix C

The use of Agent Orange was discontinued in Vietnan by the U.S. Military when the toxicity of the formulation became apparent in 1970. At this time, parts per million (ppm) quantities of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were reported as a manufacturing contaminant in 2,4,5-T; none was found in any 2,4-D product.

Young et al. (1978) reported the mean TCDD concentration of some 492 Agent Orange samples (some of these sample sources dated back to at least 1964) as 1.98 ppm (0.0247 ppm). Based on these calculations the authors estimated 368 pounds of 2,3,7,8-TCDD were released over Vietnam (The National Academy of Science 1974) estimated 220-360 pounds of 2,3,7,8-TCDD were released).

The chlorinated dibenzo-p-dioxins are a family of compounds consisting of some 75 theoretical members, each with different physical and chemical characteristics. Of the 75 possible structural configurations some 40 have been identified (Esposito et al. 1980). Several of these have been reported in the 2,4,5-trichlorophenol precursor for manufacture of 2,4,5-T herbicide formulations (Woolson et al. 1972; Firestone et al. 1972). Of these only the 2,3,7,8-TCDD isomer is known to be extremely toxic at this time (Esposito et al. 1980). Chlorinated dioxins have also been found in 2,4-D, but not the 2,3,7,8-TCDD isomer (Woolson et al. 1972; Cochrane et al. 1980).

This report reviews and examines the environmental fate of the major constituents of Agent Orange, namely 2,4-D, 2,4,5-T and 2,3,7,8-TCDD and includes summary statements on picloram and cacodylic acid which were also used as herbicides in Operation Ranch Hand.

II. Environmental Fate

Any chemical released into the environment is subject to attack by both chemical and physical forces. Chemical attack (both biotic and abiotic) can proceed by reactions such as oxidation, reduction and hydrolysis while sunlight, water and temperature simultaneously play their physical part. The extent and rate of modification of the chemical molecule is in turn dependent on the structure of that compound - the factor that predicts its chemical behavior.

Soil

2,4-D, 2,4,5-T -- These compounds have been used extensively over the past 30 years, and there is a large body of information regarding their behavior in soil. They undergo typical reactions of carboxylic acids, ethers, esters and of aromatic compounds in general (Melnikov 1971; Loos 1975; Crosby and Tutass 1966; Crosby and Wong 1973).

In early field studies, Klingman et al. (1966) reported that the n-butyl ester of 2,4-D was hydrolyzed to the 2,4-D acid within 30 minutes of application to pasture grasses; Smith (1972, 1976) also reported rapid hydrolysis of the n-butyl ester of 2,4-D in tests with clay, sandy loam and loam soils and noted that increasing the water content of these soils greatly increased the hydrolysis rate. After 24 hours no n-butyl ester of 2,4-D was present in the moist soil and no 2,4,5-T ester after 72 hours. In later work, Smith (1979) reported that in the laboratory loss rate of both 2,4-D and 2,4,5-T conformed to first order kinetics and that application of herbicide mixtures had little effect on loss rate. In these soil studies half lives were reported as follows:

Compound	Heavy Clay	Sandy Loam
2,4-D	12 days	<7 days
2,4,5-T	20 Days	14 days

Bovey and Baur (1972) applied an ester of 2,4,5-T to grassland in Texas at a rate of 0.56 and 1.12 Kg/ha and found that most of the 2,4,5-T disappeared from the soil within six weeks. Most of the initial concentration was confined to the upper 6 inches of soil (sampled to a depth of 1 meter). In addition, there was no indication of persistence or build up from year to year application of 2,4,5-T in this area. Soil studies in Oklahoma (Alton and Stritzke 1973) indicated a half life of 4 days for 2,4-D and 20 days for 2,4,5-T; in temperature controlled studies, the half life of 2,4,5-T was 4 days at 35°C and 60 days at 10°C under the same conditions (Walker and Smith 1979).

Other field and laboratory research also indicates a relatively short half life for these compounds as well as little penetration into soil. Ninety percent loss of 2,4-D and 2,4,5-T was reported in Canadian soil within 70 days of application and no residue was detected below 20 cm. (Stewart 1977). Newman et al. (1952) followed 2,4-D and 2,4,5-T under field conditions and detected no 2,4-D residue 6 weeks after application while 2,4,5-T persisted for over 19 weeks. In a water shed area, 90% of the applied 2,4,5-T disappeared in 15 days, and almost all was detected within the top 0-7.5 cm. soil layer (Lutz et al. 1973).

Radosevich and Winterlin (1977) followed the degradation of 2,4-D and 2,4,5-T esters applied at 4-5 Kg/ha to chaparral country. Over 50%

of the 2,4-D and 2,4,5-T recovered was found on soil surface litter (0-5 cm.) and 18-30% on vegetation. Up to 360 days after application, minimal residue was detected on surface litter (0.01-0.03%) and soil (0.01%). In a similar chaparral study, residues declined to 0.04 ppm 2,4-D and 0.05 ppm 2,4,5-T (all within the top 10 cm.) 12 months after application of approximately 95 ppm 2,4-D and 2,4,5-T to soil plots (Plumb et al. 1977). Forest studies show a similar degradation pattern with 2,4,5-T more persistent than 2,4-D (Norris 1966; Tarrant and Norris 1967). Following application of 2.24 Kg/ha of 2,4,5-T ester, forest floor levels declined 90% in 6 months, and after 1 year less than 0.02 Kg/ha remained (Norris et al. 1977).

Degradation studies in tropical soils also indicate rapid breakdown of both 2,4-D and 2,4,5-T. Yoshida et al. (1975) reported rapid degradation of 2,4-D in approximately 2 weeks and 2,4,5-T in 2 to 3 months in two Philippine soil types; in Hawaiian soil 2,4-D disappeared after 14 weeks, but after repeated application, disappearance took only 4 weeks (Akamine 1951).

In a study of tropical soils directly related to Agent Orange application in Vietnam, Blackman et al. (1974) came up with several conclusions on the behavior of 2,4-D and 2,4,5-T:

1. Herbicide behavior in Vietnam soils is similar to that reported for soils elsewhere.
2. Only when applied in massive amounts (1000 lb/acre) are they likely to produce phytotoxic symptoms to subsequent growth.

3. Areas where 100 lb/acre were applied may present mangrove problems but evidence of new growth was observed in heavily sprayed areas.
4. No residue was detected in areas sprayed 1.5 years before residue sampling began.
5. After one application, Agent Orange sensitive crops can be grown within 4-6 months.

Adsorption plays a critical role in the behavior of chemicals in soil, the immediate environment may occur in the anionic or undissociated molecular state. A number of investigators have reported that the presence of organic matter in soil enhances adsorption (O'Conner and Anderson 1974; Wershaw et al. 1969). However, because phenoxy compounds are weak acids, the adsorptive forces with soil particles are minimal, and the compounds are readily desorbed by water (Harris and Warren 1964; Scott and Lutz 1971). Norris (1970) reported that these compounds rapidly adsorbed to forest floor material, and that desorption was equally rapid.

Physical and chemical parameters of soil adsorption have been reported (Audus 1964; Miller and Faust 1972a,b; Grover and Smith 1974; Grover 1973; Haque 1974; Khan 1973; Koskinen et al. 1979 and O'Conner et al. 1980). All essentially agree that humic and moiety (i.e., organic matter) are important aspects in phenoxy herbicide soil adsorption, as is pH, and that adsorption data follow the Freundlich type isotherm.

TCDD - Kearney et al. (1972) studied the persistence of TCDD in sandy and silty clay loam soils in the laboratory. One year after

application of 1 to 100 ppm, 56% and 63% of the applied TCDD was recovered from the sandy and silty clay loam soils respectively. The authors emphasize that these application rates were, at minimum, one million times greater than levels that would be encountered in a 2,4,5-T application containing 1 ppm TCDD. Woolson and Ensor (1973) analyzed soil at Eglin Air Force Base, Florida, where 1060 Kg/ha 2,4,5-T was applied between 1962 and 1964. TCDD was not detected within the 1-meter deep soil profile. Harrison et al. (1979) monitored storage and loading sites at Eglin and found TCDD residue as high as 275 parts per billion (ppb), but contamination was confined to a small area.

Field plots were set up in Utah and Florida, and Herbicide Orange was injected 4-5 inches below the surface at a rate of 4000 lb/acre. Initial TCDD residue was 148 ppb in Utah and 0.375 ppb in Florida. Calculated half life for TCDD in these studies was 320 days in Utah and 230 days in Florida (Young et al. 1976). In another Eglin AFB study, Young et al. (1975) analyzed soil where 1894 lb/acre of Agent Purple (4 lb/gal 2,4,5-T) was applied between 1962 and 1964. These samples were analyzed 10 years after the last application. No TCDD was detected 6 inches below the soil surface, but residue was present throughout the 0-6 inch profile:

Depth below surface	TCDD (ppt)*
1 inch	150
1-2 inch	160
2-4 inch	700
4-6 inch	44
6-36 inch	None detected

* Parts per trillion

The National Academy of Science study (1974) also reported finding TCDD residue ranging from <1.2 to 23.3 ppb in soil from Pran Buri, Thailand, a former calibration site for Operation Ranch Hand in Vietnam.

There is little doubt from these data that TCDD is persistent in soil and that predictions on degradation are difficult to make on the basis of soil type and climate. However, persistence does appear to be confined to soils receiving massive treatment of 2,4,5-T (or TCDD). For example, rangelands and forests receiving repeated applications of 2,4,5-T at about 2 lb/acre do not appear to accumulate TCDD in the soil. This appears to be reflected in milk from cows grazing on treated pastureland where TCDD is either below detectable levels or when present at the low part per trillion (ppt) level. The same is true of tissue residue in grazing cattle and forest wildlife (Esposito et al. 1980; National Research Council of Canada 1978; Bovey and Young 1980).

Leaching and Runoff

2,4-D, 2,4,5-T - Movement of chemicals in the aqueous soil phase is fairly common and can occur in either vertical or horizontal directions. Studies with 2,4-D and 2,4,5-T indicate that only limited leaching and runoff occur except where heavy rainfall is involved (Bovey et al. 1974; Sheets and Lutz 1973).

Edward and Glass (1971) reported about 0.05% runoff of 2,4,5-T amine and only minimal percolation down through soil after applications of 11.2 Kg/ha. In a greenhouse study (pH 7.9) no 2,4,5-T was found below 35 cm. in a 150 cm. lysimeter column (O'Conner and Wierenga 1973). In plots treated with 2,4-D and receiving simulated rainfall,

White et al (1976) reported surface loss of 95% of the applied 2,4-D in 7 days, but no accumulation of 2,4-D was evident at a depth of 90 cm.

In forest studies, concentrations of 2,4-D and 2,4,5-T never exceeded 0.1 ppm in water for more than one day after application. Moreover, heavy rainfall up to 6 months later did not introduce detectable residue into streams; it was estimated that a 150 pound man would have to drink 179 gallons of this water (0.1 ppm) to ingest 1/100 of the LD_{50} for these compounds (Norris 1968; Norris and Moore 1970). Similarly, in another forest area treated with the isooctyl ester of 2,4,5-T, some residue was detected in runoff but only at levels reported to be well below the toxic level for man and fish (Lawson 1976).

Where the n-butyl esters of 2,4-D and 2,4,5-T were mixed in soils to a depth of 15 cm. (4400 Kg/ha), residues of both compounds were detected after 282 days. Even at this massive application level, 90% of the residue was detected in the top 30 cm of the soil profile. This study also indicated that downward movement was greater for 2,4-D than for 2,4,5-T (Young et al 1974). Other studies conducted in the field at normal application show that 2,4-D and 2,4,5-T remain well within the top 20 inches of soil (Bovey and Baur 1972; Smith 1975; Lutz et al 1973; Young et al 1974).

TCDD - Helling (1970) evaluated the movement of DCDD and TCDD by a soil thin-layer chromatographic technique employing five soil types and found both dioxins to be immobile. Kearney et al. (1973) observed that mobility of both of these dioxins decreased with increasing organic content of soil, concluding that both compounds were immobile in the

soil tested and probably no threat to groundwater contamination by either rainfall or irrigation.

Studies by the Air Force indicate that even with massive application and time TCDD essentially remains in the upper 6 inches of soil (Young et al. 1975). At an Eglin AFB loading site, TCDD was detected down to 1-meter; however, other sites in the same study were relatively free of TCDD contamination (Harrison et al. 1979).

Runoff and leaching do occur to some extent in areas where massive application have been made. Young et al. (1976) reported movement of TCDD to ponds at Eglin but, again, only low ppt levels were reported. Recently there have been reports of TCDD migration from chemical dump sites and landfills (Esposito et al. 1980).

Photodegradation

2,4-D, 2,4,5-T - Both 2,4-D and 2,4,5-T have been shown to undergo photochemical degradation in artificial light and in sunlight. The photochemistry of pesticides, including phenoxy compounds, has recently been reviewed by Crosby (1976).

Crosby and Tutass (1966) reported the photolytic decomposition of the sodium salt of 2,4-D in aqueous solution following irradiation in the laboratory (mercury lamp 254 nm) and in sunlight. Following mercury lamp irradiation, 2,4-D underwent rapid decomposition with 50% breakdown within 50 minutes of exposure. Analysis of the reaction mixture revealed 2,4-dichlorophenol along with 6 other degradation products, including a large amount of humic acid polymer material. Exposure to sunlight for

several days produced some of the same components including the humic acid polymer. From these data, the authors proposed a series of pathways for the photolytic decomposition of 2,4-D in aqueous solution.

Irradiation of 2,4,5-T in solution also showed that photolytic breakdown occurred but at a rate approximately one-third that of 2,4-D under similar conditions. Under artificial light, 2,4,5-T breakdown was slow with only 10% decomposition after 8 days of exposure. Isolated products included the chlorinated phenol along with intermediates and the dark polymeric humic material observed with 2,4-D. Decomposition of 2,4,5-T in sunlight was extremely slow but increased significantly when sensitizers (acetone, riboflavin) were added to the reaction mixture (80% in 2 days). Photolysis of the salts of 2,4-D and 2,4,5-T in solution appeared to produce analogous products. Photolysis of these dealkylated photoproducts was rapid (Crosby and Wong 1973; Crosby 1976).

Based on the work of Crosby and Tutass (1966) and Crosby and Wong (1973), a typical pathway for photolytic degradation begins with dealkylation to yield the phenol followed by reductive dechlorination and hydroxylation, ultimately ending in the formation of a polymeric humic material. Generation of chlorinated dibenzo-p-dioxins has not been observed in either study.

TCDD - In an early study, Crosby et al. (1971) reported rapid degradation of 2,3,7,8-TCDD and 2,7-TCDD (dichlorodibenzo-p-dioxin) isomers when these compounds were dissolved in methanol and irradiated with both artificial light and sunlight. TCDD and 2,7-DCDD were degraded by decreasing chlorine content, and 2,3,7-trichlorodibenzo-p-

dioxin was isolated and identified as a breakdown product of TCDD. However, TCDD applied to glass plates and soil did not undergo photolytic decomposition after 14 days of irradiation.

In subsequent studies (Crosby and Wong 1977), Herbicide Orange containing 15 ppm TCDD was applied to glass plates and exposed to summer sunlight. After 6 hours approximately 60% TCDD loss was observed. When applied to soil, about 85% of the TCDD remained in the soil as compared with 95% in the dark control. TCDD applied to rubber plant leaf at a rate of 6.7 mg Herbicide Orange/cm^2 of leaf surface was not detected after 6 hours exposure to summer sunlight, but at a lower application (1.3 mg/cm^2) 30% remained after 6 hours of sunlight exposure. Based on these results, the authors established three requirements for dioxin photolysis: dissolution in a light transmitting film; presence of an organic hydrogen donor; and ultraviolet light, all of which are met during the normal application of 2,4,5-T.

Aquatic Environment

The water environment includes irrigation supplies, groundwater systems, freshwater lakes and streams, drinking water reservoirs and coastal marine environments. There is abundant evidence that under normal application rates the phenoxy herbicides are short lived and do not bioaccumulate in water environments.

Bartley et al. (1970), in an extensive irrigation water study, monitored the dimethylamine salt of 2,4-D following application of 1.6 to 2.8 Kg/ha to ditch banks. Maximum 2,4-D concentration in water was 213 ppb but was below 50 ppb in over half of the sampling monitored.

Where MCPA (4-chloro-2-methyl phenoxyacetic acid) was applied to California rice pond water (1.0 kg/ha), no residue was detected in water or bottom mud 14 days after application (Soderquist and Crosby 1975).

Following treatment of a Tennessee reservoir with 22.4 Kg/ha and 44.8 Kg/ha of 2,4-D, only two water samples had detectable residues of 2,4-D (2 and 11 ppb) and no residue was detected in fish. However, 8 months after application, filter feeding mussels had levels ranging from 0.05-0.26 ppm (Wojtalik et al. 1971). Norris (1967) noted that streams traversing forested areas sprayed with 2,4-D and 2,4,5-T contained detectable residue (0.001-0.84 ppm), but levels diminished downstream. In one instance, however, 2,4,5-T residue persisted in a stream 16 weeks after application; in a marshy area ppm levels persisted for 10 days. No residues in these areas were detected 9 months later; however, the author cautioned against marsh spraying because of continual runoff into streams draining the area.

In laboratory studies designed to examine the dynamics of 2,4-D ester formulations in fresh water, Zepp et al. (1975) reported on three competing processes: chemical hydrolysis, photolysis, and volatilization and came up with the following conclusions:

1. In basic waters hydrolysis is the most important process for the methyl, 1-butyl, 1-octyl and 2-butoxyethyl esters.
2. In acidic waters the importance of the degradative process depends on the ester structure. Photolysis is the most important process for the butoxyethyl ester, vaporization for the butyl and octyl esters and both vaporization and photolysis for the methyl ester.

3. The loss rate is more rapid in basic than in acidic water.

4. The hydrolysis product of 2,4-D is resistant to chemical degradation and is nonvolatile. Therefore, photolysis is probably an important degradative pathway.

The authors calculated the half life of 2,4-D in 1-meter deep water as 20 days.

Groundwater contamination is of special concern, and a number of studies have been conducted to assess the possibility of chemical seepage into ground water supplies. Examination of Canadian farm ponds and wells revealed that 48% of the ponds were contaminated. 2,4-D was detected in 81% of the contaminated wells and 2,4,5-T in 32% of the wells. Pond residues of 6 and 11 ppb 2,4-D, and 6 and 14 ppb 2,4,5-T, were reported. All of this contamination, however, was associated with loading and dumping practices (National Research Council of Canada 1978).

Bovey et al. (1975) monitored an area treated at 2.2 Kg/ha 2,4,5-T every six months for approximately 3 years. Seepage and well water had 1 ppb 2,4,5-T residue, but no 2,4,5-T was detected in 122 drainage samples from a field lysimeter study where irrigation and natural rainfall were used to force 2,4,5-T into subsoil. O'Conner and Wierenga (1973) conducted greenhouse teaching studies with high rates of 2,4,5-T and concluded there was no danger of seepage into groundwater, particularly at lower levels.

(0.2 ppb) TCDD - TCDD is not very water soluble and therefore will behave differently in water than the more polar phenoxy herbicides.

In an aquatic model ecosystem soil was treated with ^{14}C-TCDD and residues monitored for about 4 weeks. Results suggested no degradation of TCDD and bioconcentration in exposed species ranging from 10^3 to 10^4 times the water concentration (Isensee and Jones 1975). Ward and Matsumura (1978) studied the fate of TCDD in lake water and sediment under laboratory conditions and came up with the following conclusions: TCDD is bound to sediment where it is stable and not readily available to microbial attack; very limited metabolism of TCDD occurs in the aqueous phase and metabolic products appear to be degraded more rapidly than the parent TCDD; water mediated evaporation of TCDD occurs.

Yockim et al. (1978) noted in another aquatic ecosystem study that water concentration of TCDD was dependent on the rate of soil desorption and, of course, water solubility of TCDD. Radioactivity in water from the TCDD treated soil reached equilibrium in 1 day (2-4 ppt), and bioaccumulation was noted in the organisms exposed in the system.

Young et al. (1976) examined an aquatic ecosystem draining the Eglin AFB test area in Florida where 73,000 Kg 2,4,5-T and 77,000 Kg 2,4-D were applied between 1962 and 1970. Samples collected and analyzed in 1973 had 10-710 ppt TCDD in the top 15 cm. of soil and 10-35 ppt in eroded silt that drained into an adjacent pond. The area supported a diverse fauna, and only low ppt TCDD residue levels were detected in aquatic species inhabiting the contaminated pond.

Monitoring studies have been conducted to assess the potential for bioaccumulation of TCDD in aquatic species. Baughman and Meselson (1973) reported TCDD residues in fish and crustacea from Vietnamese

waters; however, residue studies did not show TCDD contamination in a wide variety of aquatic species in Canada (Zitko 1972) or in a rice growing region of the U.S. where 2,4,5-T had been applied annually for 20 years (Shadoff et al. 1977). In addition, Bowes et al. (1973) did not detect TCDD in marine birds, mammals and fish species considered to be at the top of their respective food chain, suggesting that bioaccumulation of TCDD occurs but not biomagnification to the top tropic level as seen with DDT.

Studies on the behavior of TCDD in aquatic environments suggest that degradation occurs, but where high amounts have been introduced, persistence in sediment and water (by desorption) may be a problem. Bioaccumulation occurs but apparently not biomagnification to the top tropic level. Based on its nonpolar nature, one would expect TCDD to adsorb to particulates or sediment and partition into organic substrate. While available information tends to support this behavior pattern, more information is needed on the dynamics of TCDD (industrial effluents, drinking water supplies) in the aquatic environment.

Microbial Degradation

2,4-D, 2,4,5-T - Microbial degradation is certainly of major importance regarding the fate of phenoxy compounds in the environment, and numerous studies have reported on this degradation and detoxification. Early work by Newman et al. (1952) and Audus (1964) indicated that 2,4-D disappeared in 2 to 3 weeks while 2,4,5-T persisted anywhere from about 6 to 40 weeks in soil. Hammett and Faust (1969) noted that

biodegradation of 2,4-D followed zero-order kinetics and that the oxidation rate was independent of the substrate concentration.

Audus (1960) reported that it took 20 days for 80% breakdown of 2,4-D in soil treated at a rate of 100 ppm, but after retreatment 80% breakdown occurred in only 3 days. Torstenson et al. (1975) studied the effects of repeated applications of 2,4-D and noted a reduction in degradation time from 10 weeks to 4 weeks after 19 years of annual application (20 weeks to 7 weeks for MCPA).

Under generally similar conditions, 2,4,5-T appears to persist about 3 times longer than 2,4-D. McCall et al. (1981), for example, reported an average 50% degradation time (in six soil types) of 4 days for 2,4-D and 14 days for 2,4,5-T while 90% degradation of 2,4-D took 11 days and 2,4,5-T, 42 days. The half life of 2,4,5-T in forest soil was estimated to be 7 weeks (Newton 1971). In tropical soils Blackman et al. (1974) reported that phytotoxic residues of the n-butyl esters of 2,4-D and 2,4,5-T were not evident after 4 weeks. Rosenberg and Alexander (1980), however, reported little loss of 2,4,5-T in four tropical soils after 2 months. Of 52 bacterial groups isolated from soil and sewage, the authors found 41 that degraded 2,4-D and 2,4,5-T but only through cometabolism.

Microbial resiliency was exemplified by Young (1980) who reported that areas of Eglin AFB receiving 76,000 Kg/ha 2,4-D and 75,000 kg/ha 2,4,5-T from 1962 through 1970 had microbial populations similar to those from adjacent control areas. Moreover, studies in Utah where soil levels reached 10,000 ppm, a half life of 150 and 210 days was

reported for 2,4-D and 2,4,5-T. Stojanovic et al. (1972), as well as others, have observed that a mixture of the two compounds degrades faster than when the compounds are used alone.

Degradation pathways for phenoxy herbicides by microorganisms have been reviewed by Loos (1975). The major pathway for degradation of 2,4-D and MCPA by an Arthrobacter sp. and pseudomonads is by removal of the acetic acid side chain to yield the corresponding phenol. This is followed by ortho hydroxylation to form the catechol with conversion to the muconic acid and subsequent cleavage of the aromatic ring. Elimination of the 4-chlorine with replacement of hydrogen has also been postulated. There is also evidence that a pseudomonad hydroxylates the 6 position on the aromatic ring forming 2,4-dichloro-6-hydroxyphenoxyacetic acid.

Rosenberg and Alexander (1980) in labelled studies reported that cometabolism of 2,4,5-T led to chloride release and formation of phenolic products as well as cleavage of the ring. A pseudomonad soil isolate in this study degraded approximately 70% of the 2,4,5-T in 80 hours and approximately 60% was recovered as phenol.

2,4,5-trichlorophenol was converted in soil suspensions to 3,5-dichlorocatachol, 4-chlorocatechol, succinate and several tentatively identified products. The 3,5-dichlorocatechol product was also postulated by Horvath (1971) working with Brevibacterium sp. McCall et al. (1981) reported two major metabolites formed from microbial breakdown of 2,4.5-T. These included formation of the 2,4,5-trichlorophenol followed by microbial methylation to produce 2,4,5-trichloroanisole, but analogous metabolites were not observed for 2,4-D. The anisole was quite volatile with a 50% loss from

soil in 1 to 3 days. Degradation of 2,4-D was reported to be so rapid in this incubated system that intermediate products were difficult to isolate and identify.

Microbial degradation of TCDD in soils does not appear to be a rapid process. Matsumura and Benezet (1973) screened 100 microbial strains known to degrade chlorinated pesticides and found only five strains capable of degrading TCDD. Kearney et al. (1972) also reported that TCDD was not readily metabolized by soil organisms since the half life approximated 1 year. Helling et al. (1973) concluded from these studies that TCDD persistence would be expected since it is an insoluble, nonpolar, chlorinated molecule without biologically labile functional groups.

Pocchiari (1978) in tests with Seveso soil attempted to induce degradation by inoculation with microorganisms showing some ability to degrade TCDD; very minimal success was achieved. The absence of TCDD residue in the Lakeland soil of one study (Woolson 1973) where massive application occurred does suggest, however, that microbial degradation does occur. For the most part, however, it appears that microbes are not capable of rapid and complete elimination of soil or sediment bound TCDD residues.

Plants

Persistence and disappearance of 2,4-D and 2,4,5-T from plant surfaces has been monitored in a number of field studies. Klingman et al. (1966) applied high and low volatile esters of 2,4-D to pasture land at a rate of 2.24 Kg/ha and noted that forage residues declined

rapidly from 58 ppm to 5 ppm in 7 days. The authors also noted that 75% of the butyl ester was hydrolized to the acid 30 minutes after application. Bovey et al. (1974; 1975) reported no accumulation of 2,4,5-T in vegetation following approximately 3 years of semiannual application within the same area. Initial residues after treatment were high (28-113 ppm) but disappeared before the following application. Morten et al. (1967) also reported no build up of either 2,4-D or 2,4,5-T on vegetation after repeated application. Green tissue had a half life of about 2 to 3 weeks for both compounds with grasses averaging a little longer at 3 to 4 weeks.

In a semi-arid area considered poor for rapid breakdown, maximum concentrations of 2,4-D (95.2 ppm) and 2,4,5-T (92.4 ppm) were detected on chaparral vegetation 15 minutes after application but dropped rapidly and then remained at about 4 ppm 2,4-D and 3 ppm 2,4,5-T after 12 months (Plumb et al. 1977). Radosevich and Winterlin (1977), in a similar chaparral study, sampled up to 360 days after application of 4.5 Kg/ha of esters of 2,4-D and 2,4,5-T. They noted that 90% of the initial foliage residue disappeared within 30 days after application and then remained constant until winter rainfall. At 360 days approximately 0.01-0.02% of the initial foliage residue was detected.

In addition to photodegradation, volatilization, microbial attack, and wash off, 2,4-D and 2,4,5-T are also subject to uptake and metabolism by plants. With few exception, there appears to be little persistence in plants, but in some woody species, low level residues have lasted for more than 5 months. For most plants, however, 1-3 weeks

appears to approximate the half life of these compounds (National Research Council of Canada).

TCDD - Oats and soybeans grown in TCDD treated soil accumulated less than 0.15% of the TCDD soil concentration, when leaves were treated, no translocation beyond the leaf was detected (Isensee and Jones 1971). In addition, 94% of the TCDD applied to the leaf surface of soybeans remained there for 21 days, while residue on oat leaves continually decreased. In a similar study using sorghum, TCDD uptake from soil was reported to be one millionth of one percent of the TCDD in the soil (Bovey and Young 1980). Residue data for TCDD and plants is especially incomplete. However, the study of Crosby and Wong (1977) indicates rapid photolytic degradation of TCDD in Herbicide Orange on rubber plant leaves by sunlight with a half life of 1-2 hours (6.7 mg herbicide mixture/cm^2).

Volatization and Atmospheric Residue

2,4-D, 2,4,5-T - All ester formulations of 2,4-D and 2,4,5-T are volatile but vary in rate of volatility; amine and sodium salt formulations have little or no volatility problem. Baur et al. (1973) found 55% loss of applied 2,4,5-T at 60°C but no loss after 7 days at 30°C. Baur and Bovey reported dry preparations of 2,4-D subjected to 60°C resulted in over 50% loss of the compound in one day. Grover et al. (1972; 1973) reported vapor losses of 30% and 13% for butyl and isooctyl esters of 2,4-D in field studies.

Que Hee and Southerland (1974) reported volatility of the butyl esters of 2,4-D when applied as a thin film or drop on glass or leaf

surfaces increased directly with the available surface area to applied mass ratio and inversely with the adsorptive capacity of the surface. Grover (1976) conducted volatility studies in a closed flow system and reported the following rates of volatilization for esters relative to the nonvolatile 2,4-D amine salts (assigning the nonvolatile amine salts a value of 1):

Classification	Ester/salt	Relative rating
High volatile (HV)	mixed butyl	440
Low volatile (LV)	propylene glycol butyl ether	33
	butoxy ethanol iso-octyl	
Non-volatile (NV)	mixed aminex dimethyl amine diethanol amine	1

Grover et al. (1972) reported that 20 to 30% of the butyl ester of 2,4-D was collected as vapor drift after field application whereas little or no 2,4-D amine used in the same study was detected.

Phenoxy herbicide residues have been detected in air in areas where these compounds are used fairly extensively (Vernette and Freed 1962; Grover et al. 1976; Que Hee et al. 1975); Elias (1975) reported detecting residue of the butyl ester of 2,4-D at an altitude of 3000 feet. Data on volatilization and drift during defoliation use in Vietnam are not available, however, data available in this country and in Canada indicate volatilization and drift did occur. This is supported by Young et al. (1978) in their summary of the environmental fate of phenoxy herbicides in air during project Ranch Hand in Vietnam.

TCDD - Matsumura and Ward (1978) reported that water-mediated evaporation of TCDD may take place based on laboratory study. Esposito et al. (1980) cite a ^{14}C TCDD study conducted in a microagrosystem which indicates TCDD has a very low vapor pressure and that loss due to volatilization is very low. This is borne out in studies by Crosby (1971) and Crosby and Wong (1977) where TCDD was found to be relatively stable and persistent (at least up to 14 days) in soil and on glass plates unless requirements for photolytic degradation were supplied.

Currently, the generation of dioxins in fly ash from incineration of municipal wastes as well as from dispersal of particulates from dump sites is being investigated (Esposito et al. 1980).

Picloram and Cacodylic Acid

Approximately 3 X 10^6 pounds of Picloram (4-amino-3,4,6-trichloropicolinic acid) were released in Vietnam between 1962 to 1971 as the active ingredient in Herbicide White (Young et al. 1978). Picloram appears to be a relatively safe compound having low toxicity for man and other mammals, birds and fish. It is very sensitive to volatilization and can be easily leached from soil by rainfall. Soil losses ranging from 56 to 96% over one year's time are reported. It is only slightly photolabile and undergoes microbial breakdown only at a slow rate (Foy 1975).

Cacodylic acid (hydroxydimethylarsine oxide) was the active ingredient in Herbicide Blue, and some 3.5 X 10^6 pounds were used in Vietnam between 1962 and 1971. The degradation of cacodylic acid in soil is not well researched even though this compound has been used extensively over the years. It apparently degrades aerobically in soil to a volatile

organoarsenical and to a second compound by cleavage of the C-As bond(s); anaerobically, only the volatile compound is formed. Degradation in soil is apparently slow and cacodylic acid forms insoluble compounds in soil. This compound is considered to be moderately toxic (Woolson, 1975).

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Science Panel
March 5, 1982

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date March 5, 1982

From Chair, Science Panel
Agent Orange Working Group

Subject Review of the Veterans Administration Epidemiology Study Proposed Protocol

To Mr. James Stockdale
Chair, Agent Orange Working Group

The review of the proposed protocol submitted to the Veterans Administration by the University of California at Los Angeles is enclosed.

In summary, on the basis of the present document, the panel believes it is possible to begin the pilot phase of the study. (1) The selection of the cohort for the Pilot Study should immediately proceed as well as the (2) quality control and quality assurance procedures, (3) the redesign of the questionnaire, (4) and the determination of comparability and interpretation of some of the proposed instruments, such as nerve conduction studies, spirometry, etc., between examining centers. Finally, we believe that major progress has been made in the past several months and that it is now possible to do the Veterans Administration Epidemiology Study, looking not only at Vietnam exposure but exposure to Agent Orange. We view as the only remaining factors that will prevent the successful completion of this study to be the degree of participation among the selected veterans and the nonavailability of necessary resources.

We recommend you transmit the consensus document and the individual comments to the Veterans Administration.

Vernon N. Houk, M.D.

Enclosure

cc:
Mr. Maurice LeVois

AGENT ORANGE WORKING GROUP
SCIENCE PANEL REVIEW OF PROPOSED PROTOCOL DESIGN
FOR VETERANS ADMINISTRATION EPIDEMIOLOGY STUDY

By School of Public Health
University of California at Los Angeles

The following represents a consensus of the reviewers of the proposed protocol design. All reviewers were present except one and his detailed comments were made available to the other members. The individual comments are enclosed (Tab B).

Overall Design

We agree that the historical cohort approach is the appropriate one. One member suggested more consideration be given to a case control approach but all other reviewers felt this is not possible because there is no clear cut definition of a "case." We also agree with the approach to try to make it as compatible as possible with other large studies such as the Ranch Hand and the Australian Study.

COHORT

Selection

The panel unanimously agrees that the Department of Defense (DOD) should select the cohorts in accordance with Dr. Bricker's cohort selection paper (Tab A). This will provide, we believe, for elimination of as much misclassification as is possible from the existing or potentially reconstructable records. We believe it is absolutely essential that the identification and assignment of these individuals to the different cohorts not be available to the participants or to the investigators until initial analysis of the data is completed. The Science Panel will oversee this cohort selection process. The study investigators must be aware of the method used to select the cohorts but must not be aware of the individuals placed in each group.

Criteria For Each Group

We recommend that groups be composed of high probability of exposed Vietnam veterans, high probability of nonexposed Vietnam veterans, and a non-Southeast Asia veterans group. Some felt that it would be desirable to include a Vietnam veterans group exposed midway between the first and second groups in order to make an assessment of dose response. The consensus is that though this may be desirable, the inclusion of the fourth group is not essential nor critical to the study.

Sample Size

We agree that 6,000 in each cohort group is a reasonable figure. As the study progresses and as more information becomes available from other studies, this issue may need to be reexamined. DOD anticipates being able to provide 12,000 in each of the study groups for selection.

Proposed Exclusions from the Cohort Group

We believe it is unreasonable to exclude officers and multi-tour Vietnam veterans. These may be separately identified so that appropriate analysis can take place but they should not be excluded from the study.

QUESTIONNAIRE

Questionnaire to Personal Health Providers of the Individual Veterans

Some of the selected veterans may have had multiple health care providers since returning from Vietnam. The panel doubts that many private physicians will fill out detailed questionnaires on their patients and thus wonder about the usefulness of this part of the study. The needed information may have to be obtained in other ways.

Individual Veteran Questionnaire

The questionnaire as it now exists is unacceptable. It is overly long and uses highly technical terminology which many people including many physicians will not understand. We recommend that careful thought be given to the information that is needed to be gathered, who will administer and where the questionnaire will be administered (telephone, home visits, etc.), and that the questionnaire be redesigned to meet those criteria. The questionnaire should be limited to information that is critical to the study and that will be used in the analysis of the results.

Other Instruments

The psychological and neuropsychological instruments, all of which were not available for review, should be evaluated and should include only information that will be used in the analysis of the results and presented in a way that would not be offensive to the participants.

Physical Examination

Data collected from the physical examination should be limited to those items that will be used in the analysis of the study. This does not mean that the physcial examination should not be comprehensive as determined by the examining physician for the particular individual, although items to be used for analysis of results must be collected according to a standard protocol.

Laboratory

The final decision for the inclusion of laboratory tests for this study should be made after consultation with laboratory scientists to ensure that the best tests for that particular purpose are being used. There are other tests such as chest x-ray, spirometry, nerve conduction tests, etc., that probably have limited usefulness because of the inability to standardize and to intrepret between multiple examining centers.

It is critical that the standardization of laboratory procedures proceed with quality control and quality assurance for collection, transportation, handling, and analysis and that this process be begun immediately in the participating laboratories.

Other Areas of Concern

For all participants, the panel believes that information should be collected only on those items that are critical to the study, can be standardized, and are such to appropriately interpret between multiple examining centers and laboratories. If the practising physician feels that additional information is necessary for a particular patient to evaluate the health status, it obviously should be done but should not be part of the overall data collection and analysis for the purposes of this study.

It is not clear from the proposed protocol the duration of the overall study or time estimates for each individual participant. These should be determined. A possibility that should be considered in regard to future duration is that after completion of the initial examination and analysis, the cohorts names be matched against the National Center for Health Statistics (NCHS) Annual Mortality Index. This would provide nearly all of the necessary followup information and would be more efficient than a mail survey or a hands-on followup of each individual.

It should be explicitly stated in the final design that when an abnormality for an individual is found, how that abnormality will be followed, who will follow and treat it, and what system will be set in place to ensure that each individual will receive the necessary medical care.

After the initial analysis has been completed and depending upon the results, additional well focused, smaller studies, such as specific case control studies, may be necessary to further define the extent of possible uncovered problems.

After the initial analysis has been completed, the method of cohort selection should be made public. While still ensuring individual confidentiality, each participating veteran should be informed of his or her status in the cohort selection process.

The panel assumes that the final protocol will address the usual concerns of patient confidentiality, freedom to withdraw from the study, and methods of providing the individual veteran specific medical information of which he or she or his or her physician should be aware for the proper care of the individual veteran.

Pilot Study

We believe the Pilot Study should include 5 percent of the anticipated study population. We recognize it may not be possible that this be a random sample of the population but that it be clearly stated and understood what that 5 percent represents. The panel unanimously disagrees that the Pilot Study should take place in only one study site but recommends strongly that it be conducted in all examination centers and study sites that will

be used in the overall study. The Pilot Study should be used to determine participation rates and to further refine the instruments to be used in this study. An analysis of the results of the pilot study can be used to make a determination of the possibility of success of the larger study. The results should in no way be interpreted as to effects but only whether it is possible to conduct a scientifically valid overall study.

Summary

On the basis of the present document, the panel believes it is possible to begin the pilot phase of the study. The selection of the cohort for the Pilot Study should immediately proceed as well as the quality control and quality assurance procedures, the redesign of the questionnaire, and the determination of comparability and interpretation of some of the proposed instruments, such as nerve conduction studies, spirometry, etc., between examining centers. Finally, we believe that major progress has been made in the past several months and that it is now possible to do the Veterans Administration Epidemiology Study, looking not only at Vietnam exposure but exposure to Agent Orange. We view as the only remaining factors that will prevent the successful completion of this study to be the degree of participation among the selected veterans and the nonavailability of necessary resources.

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D.C. 20301

HEALTH AFFAIRS

4 DEC 1981

MEMORANDUM FOR THE CHAIRMAN, AOWG SCIENCE PANEL

SUBJECT: Proposed Agent Orange Troop Exposure and Non-Exposure Cohort Selection Concept Paper

For many months the Science Panel as well as the Agent Orange Working Group (AOWG) has researched many avenues to seek out a plausible means to establish reasonably exposed and non-exposed field troops in Vietnam with respect to herbicide orange spraying. Public Law 96-151 mandates an epidemiological study to endeavor to determine if exposure to Herbicide Orange (2,4-D, 2,4,5-T, 50/50 mix with the contaminant 2,3,7,8-TCDD) caused deleterious health effects among exposed military personnel.

The following concept paper presents a proposed methodology to identify research cohorts by using three large groups of military personnel. The first group of approximately 12,000 people would constitute a relatively heavily exposed ground troop population serving in Vietnam; the second group, also of 12,000, would serve as a non-exposed Vietnam troop population; and the third group of 12,000 would be personnel in the military service stationed in the southern part of the United States in the same time period. The second group of non-Herbicide Orange exposed Vietnam veterans is considered very important from the standpoint of determining whether other chemicals, diseases and toxins (e.g., aflatoxin B) present in Vietnam may be the source of illnesses and symptoms affecting those veterans who have filed claims. This paper (with its tabs) will sequentially discuss the factors which contribute to a typical herbicide exposure and how they might have affected the ground soldier operating in the tropical jungles of Vietnam. After establishing the necessary technical background information, we will proceed to address how an exposed population may be found and how we may in some measure determine a potential degree of exposure. Next a proposed method of locating an unexposed serving-in-Vietnam population will be presented. Pentultimately, we will provide a brief discussion of the technique to select a non-exposed, non-service in Vietnam control group having similar demographic characteristics. Finally, and perhaps most importantly, a technique will be advanced to secure (by means of the use of information already on file in the Veterans Administration Agent Orange claim file) a verification program to assure the concerned veterans organizations that truly highly exposed military units have been selected as the study population.

Exposure Considerations

Although a large quantity of herbicides were sprayed by Ranch Hand aircraft from 1965 through 1970 including a preponderance of Herbicide Orange, the question still remains as to actually how much of the herbicide reached the ground to 8 ft level of the dense forests. Studies have shown that about 13 percent of the herbicide released at 150 ft. altitude from a C-123 flying at 150 knots is vaporized into the air or drifts away as a cloud before the droplets hit the top layer of the forest. Hence, the original aircraft load of 1,000 gallons is immediately reduced to 870 gallons. The remaining 870 gallons are then disseminated over a distance of 14 kilometers or 8.96 miles. The swath width per aircraft has by testing been determined to be 260 $\pm$ 20 feet, hence the area covered per aircraft with these 870 gallons is 5,280 ft/mile X 260 ft X 8.96 miles = 12,300,288 square feet covered by one aircraft spraying 870 gallons of Orange. This would give a concentration of herbicide of .0000707 gals/sq ft on top of the jungle canopy. However, in a dense 3 layer jungle canopy such as the ones defoliated in Vietnam, the layers of foliage entrapped and absorbed 84 percent of the 350μ size droplets. The lowest level of foliage was anywhere from 15 to 25 feet above the floor of the jungle. Foliage impingement and absorption reduces the concentration of herbicide reaching the ground zone (0 to 8 ft) by 84 percent. This results in concentration of droplets entering the 0 to 8 ft above ground zone to .0000042 gal/sq ft. (100% - 84% X .0000707 gals/sq ft). Converting gallons/sq ft to ounces/sq ft we have (.0000042 X 128 oz/gal) giving a concentration of .0005376 oz/sq ft. Five ten-thousandths of an ounce per square foot is a very small amount if it contained 2 ppm of TCDD.

Other factors acting over time to reduce residual herbicide on the foliage include absorption of Orange into the plants within 30 minutes from these size droplets. An ultra-violet half life of TCDD in the presence of 2,4-D and 2,4,5-T (hydrogen donors) of about 6 hours with conversion to less toxic tri- and di-chlorodibenzo dioxins also would reduce the concentration of TCDD present on sun exposed leaves. Further, TCDD has been shown to have an extremely low vapor pressure and an even lower solubility in water (2.0×10^{-7}). Herbicide foliage coverage and absorption rates are confirmed by the profound leaf kill and leaf drop effects produced on the top cover foliage even when rain occurs within an hour after the spray mission (pre-1965 testing, Kontum). Comparing the concentration of penetrating herbicide at the 0 to 8 ft level by another means it comes to about .166 gallons/acre. Here in the United States it was customary to apply 2,4,5-T in agricultural use at the rate of 2 gallons per acre.

Because of the aforementioned experimental factors, it does not appear that even if an individual were directly under a triple level

jungle canopy during a Ranch Hand spray run that he would receive a total body dose on his uniform of more than .0000084 gal/head and shoulder area (.0010752 oz/man's area) especially if he remained still as the droplets would fall almost vertically. He might be able to increase his clothing dosage if he ran rapidly through the forest in the direction toward the aircraft flight path, however, that would be difficult in a dense jungle because of the underbrush.

We should note, however, that not all of the areas defoliated by Ranch Hand aircraft were dense tri-canopy level jungle forests. Also, Ranch Hand aircraft resprayed the same forests after the top canopy had been removed by earlier spray missions. Hence, in these situations the herbicide droplet penetration to ground level would be much greater. Likewise, the secondary cloud drift and evaporation would also increase as the droplet fall distance is considerably extended (3X). Unfortunately no test data has been located which will give us reliable experimentally determined vaporization and secondary cloud effects. Some reports by Dr. Minarik of Fort Detrick give an evaporation rate of 3 percent for Orange. Air Force presentations listed up to 13 percent loss from small droplet cloud generation and evaporation as the spray hits the turbulent airstream from the aircraft. From studies by Minarik, about 12 percent of the droplets are smaller than 200μ in diameter. Droplets less than 200μ are more subject to drift and can travel up to 1,584 feet from release line. Smaller than 100μ droplets can travel up to 1 km. laterally from the line source before impacting on plants or ground.

Therefore, troops under sparse canopy or relatively open forests could receive as high a concentration of Orange as .0000707 gals/sq foot. Converting .0000707-gals/ft^2 to ounces/ft^2, we find a concentration of .00905 oz/sq foot at the ground. Our individual soldier standing in an open area would thus receive a droplet dose of .0181 oz of herbicide in the form of very small ($< 300\mu$) droplets on his head and uniform. There does not appear to be any way to estimate what his inhaled dosage might be as so many variables come into play.

On the other hand, perimeter spraying of fire bases and camps was a much less rigidly controlled operation than Rancn Hand flights. Helicopter spraying movies prove that spraying was conducted over populated fixed positions, armored personnel carriers, and guard towers. Contrary to earlier beliefs Herbicide Orange was also utilized in considerable quantities around bases and along lines of communication. Helicopter spraying was at low altitudes over areas which had already been cleared of high trees, thus the surface contamination at ground level would likely be much heavier due to the rotor blade downwash, lack of tree foliage absorption, and close proximity to stationary troop locations. Add to this the employment of ground spraying apparatus such as by use of chemical agent

decontamination spray trucks (600 gallons at 800 lb/in^2 pressure), hand sprayer back-pack apparatus and Buffalo turbines (150 mph air blast at 10,000 ft^3/min volumes finely atomized) and we have several sources of unregulated droplet and aerosol spray devices. Military movie and other photo coverage indicates that it was common to spray fire base perimeters at about 5 week intervals. Since usually all sides of the perimeter would be sprayed regardless of the wind direction some spray drift over troop inhabited areas would be expected. Because of the need for clear fire zones to prevent infiltration of the firebases free spraying commonly was practiced. This in my opinion would be a much closer and far more concentrated exposure to herbicides than for troops under a dense jungle canopy being sprayed by C-123 aircraft. There also would probably be a greater respiratory and residual artifact contamination source for percutaneous and alimentary absorption of the herbicide. It was surprising to find that some units kept fairly accurate records of perimeter spraying dates, however, they frequently failed to note the gallons used and the type of herbicide. Times of application varied much more than the dawn or dusk regimen of the Ranch Hand operational spray missions. For the aforementioned reasons, any highly exposed sample of personnel would have to include repetitious ground spraying of the unit's base camp and fire bases to ensure additional exposure beyond that encountered from Ranch Hand mission proximity.

A third but extremely frequency limited source of exposure could result from low altitude jettison of herbicide cargoes from C-123 aircraft under dire emergency conditions. The C-123 10" dump valves were capable, when fully operable, of dumping 1,000 gallons within 30 seconds. This would empty the tank in a distance of 1.33 miles with no control of droplet size compared to the usual boom spray dissemination line of 8.96 miles. The concentration during a maximum jettison would therefore be about 6.74 times more concentrated for the shorter line source providing that all of the agent reached the ground. The ground dosage would vary with release altitude and meteorological conditions. However, here we encounter problems concerning how much liquid herbicide would pass through the atmosphere and reach the ground to contaminate ground troops. Possibly, if the herbicide dump took place at 3,000 feet or more (minimum altitude to avoid effective small arms fire hits) most if not all of the agent would evaporate before reaching the ground or drift for long distances as a diluting cloud. This opinion is based on the 13 percent evaporative loss and cloud drift experienced at very low altitude runs just above the jungle canopy. So far we have been unable to find any actual test data to confirm or deny whether herbicide released from high altitude would reach the ground. Early (before 1961) large area crop destruction testing showed an altitude of 1,000 to 1,500 ft to be the optimum altitude for maximum crop area coverage of very small size droplets ($\leq 100\mu$). But if the herbicide were released at 500 feet or less altitude in dense

concentrations (10" dump valve orifice) the per foot concentration would be .1424 gallons assuming uniform release distribution (not necessarily true because of hydrostatic pressure variance with time). Under this situation probably liquid herbicide would reach the ground surface. Wind velocity, aircraft speed, ambient temperature and humidity, and wind direction would further affect evaporation and dispersion of the herbicide before it reached the ground. It would, however, be possible if considered necessary to run actual dump testing at a remote location such as Dugway Proving Ground using still available Air Force Reserve C-123s and the A/A45Y-1 tanks and booms. I would recommend that the same Herbicide Orange formulation be used to ensure accurate results from altitude drops at varying heights. The matter of obtaining EPA clearance could be a problem for such a test.

When seeking a heavily herbicide exposed troop concentration, it would seem wise to include units which were under or in close proximity to low altitude orange jettisons. Any dumps over air bases or troop encampments should be especially considered as exposure sources. These dumps are the third criteria in establishing a high troop exposure index in the proposed methodology.

Possible Heavy Orange Exposure Cohort Selection

The large area spraying of herbicides, especially Herbicide Orange, by fixed wing aircraft seems to be of continuing urgent concern to most of the veterans' organizations. Most of the press coverage has also focused on this particular aspect of herbicide use even though the area covered in Vietnam was limited to 10 percent of the major land mass and the proportionate poundage was considerably less than the amounts of similar herbicides produced and sold in the United States during the same period (approximately 110 million pounds). Because of the worldwide constant use of 2,4,5-T since the end of the 1940s to the early 1970s, it may be impossible to find any group of persons who have not had some exposure to dioxin if they are older than 10 years. As other records obtained from GSA show there were 36 different combinations of phenoxy herbicide stock numbers available in various packaged quantities for Federal agency use. Therefore, as suggested in our Science Panel meetings, it may be a matter of total degree of exposure rather than being able to find a truly unexposed cohort. The recent EPA findings of dioxin presence in adipose tissue of six persons at autopsy in rural Ohio lends credence to this postulation as does the presence of dioxin in fish in the Great Lakes and dioxins in the stack gases from a municipal waste incinerator.

Even though these serious confounding factors exist within our whole environment we should still focus on choosing units which were in relatively close proximity to Herbicide Orange fixed wing spray tracks during a selected year. This, with some degree of precision,

was accomplished in the initial battalion studies in which company size units of the 1st of the 9th Air Cavalry were located as having been within one kilometer of a herbicide spray track within seven days of the date of spraying. With further alteration of the computer matching program we could perhaps narrow the time interval to one day for exposure proximity. The selected battalion already studied had a personnel turnover of 2,400 men in the one year studied, thus four more comparably sized units could provide a sample cohort of 12,000 exposed persons. These other battalion size units may be initially screened for herbicide exposure by picking only those organizations which were assigned to areas in which maximum spraying activities took place as shown by our fixed wing spray map overlays. Perhaps an additional 8 to 10 battalion studies would need to be undertaken to select the five most highly exposed battalion size units. Marine battalions should also be reviewed and unit locations compared to herbicide tracks.

Selection of 10 battalions with multiple close proximity locations to fixed wing spray tracks would complete step one criteria qualification of the highly exposed 12,000 member cohort out of a possible complement of 24,000 personnel from 10 battalions. See Tab A for a graphic representation of how these units might meet the step one criteria by dates of close Ranch Hand spray tracks as obtained by the computer matching program used in the earlier battalion studies.

Next these ten battalions would be examined under the step two criteria. Step two involves a detailed review of the records of each base camp and fire base occupied by each unit of each of the 10 battalions to determine how often, and when the base perimeters were sprayed with Herbicide Orange. This would be a particularly important step for reasons mentioned in the background section of the paper (potential high close exposure). Spray frequency dates for herbicide perimeter spraying would be recorded for each of the 10 battalions during this same one year period. The third column of Tab A presentation shows how this could possibly develop a series of spray date listings of exposures.

Battalion size units (10 battalions) meeting both step one criteria (heavy fixed wing spray proximity) and step two criteria (frequent perimeter sprayings of base camps) would then be examined for qualification in meeting step three criteria. Step three criteria would be that units of the battalion had to be encamped or operating within 2 kilometers of a Herbicide Orange low altitude emergency jettison. A two kilometer range was selected since an aerosol concentration to this distance from ground zero would be fairly likely from such a massive spill (see background section). It should be remembered that it would be a line source (1.3 miles) rather than a point source. The only exception would be from an aircraft crash without ensuing fire. No computer printouts of any

accuracy are available for determining either Criteria 2 or Criteria 3 qualification, hence manual checking from paper records and map plotting would be necessary. The probability of achieving Criteria 3 qualification because of low frequency of low altitude dumps would be slim resulting in the presentation shown in Column 4, Tab A.

Proposed Unexposed Vietnam Combat Cohort

As stated earlier, location and positive verification of unexposed units may be the most difficult aspect of the unit selection process. Non-qualification under Criteria 1 may not be as difficult as earlier thought. National Academy of Science Study computer map overlays drawn by calendar years for crop and defoliation missions show entire provinces which were never sprayed by fixed wing aircraft in a one year period. Therefore, units operating exclusively in these non-sprayed provinces would be initially selected. Again ten battalions (hopefully with a total troop complement of 24,000 persons) would be selected. After qualification of units by not meeting Criteria 1, the expected most difficult part of the selection process under Criteria 2 would be attempted. Our proposed approach for locating non-Criteria 2 qualified units (those not exposed to any local perimeter herbicide spraying) from the 10 battalions selected above would be to seek units far removed from major supply centers, really out in remote hamlets at the end of the logistics supply chain. Here the hope is that unit supply was so difficult that mainly ammunition, food and medical supplies took priority and hence there was no room to send along herbicides for use in perimeter spraying or the use of herbicides would not be needed for defensive purposes. We would also look for units who were both base camp support party and those operating out in the jungle such as Special Forces or Ranger units. The selected units must however be exposed to the indigenous diseases and other hazards of the jungle and be using protective measures such as insecticides, insect repellent, and preventive malarial medications. They also should be using the full spectrum of weapons including riot control chemical agents, etc. This selection for non-qualification under Criteria 2 may be quite laborious and require more than 10 battalion surveys, but consider it to be very critical in producing a valid study and solution to our vexing problem of exactly what is or are the sources of illnesses. Non-qualification of Criteria 3 of those units who non-qualified under Criteria 1 and 2 should be very easy as most of the herbicide jettisons from C-123s took place in the combat spray area or near their operating bases, hence they would be nowhere near these remotely located companies. As in the highly exposed cohort we would strive for a minimum cohort size of 12,000.

Proposed Non-Exposed, Non-Vietnam Control Cohort

One prime criteria with several secondary criteria would apply to this "Control" cohort. The prime criteria would be that no members of this group would have ever served in Vietnam or other areas of Southeast Asia including Thailand. Secondary selection criteria would include young males of the same age ranges as the test population and of the same general racial distributions. We believe a suitable 12,000 member cohort meeting these criteria could be located for the 1967-1969 period from either Fort Benning, Georgia or Fort Hood, Texas. Records of these posts could be checked to determine if the post engineers had utilized any 2,4,5-T in the troop areas during the sampling time frame (1967-69).

Proposed Validation of Selected Cohort Samples

Validation in the context of this proposal would be a form of assurance to the concerned veterans that a likely heavily exposed group of veterans had been selected for study. The information to accomplish this must come from the Veterans Administration (VA) which receives input for and maintains the Agent Orange Registry (AOR) consisting of names of veterans who have filed claims regarding personal effects from herbicides. From the available input forms and claims forms supplied by the VA, it appears that a necessary and valuable sequence of information pertaining to Vietnam service has not been obtained from these veterans claiming harmful effects. The information which is needed consists of the individual military assignments and the dates of same while the individual was serving in Vietnam. We understand that the entire AOR contains approximately 67,000 names, however, there is a secondary group of persons who have filed claims numbering about 12,000. This latter group would be used to validate the heavily exposed cohort and also the non-exposed service-in- Vietnam cohorts. The entire comparison would be based on knowing each individual's unit assignments and dates of assignment. Two possible ways appear feasible for obtaining the desired unit assignment information. These methods are described in the following paragraphs:

Method 1.--The VA would provide the 12,000 name listing, including the man's full name, social security number, service number, and date of birth, to the Department of Defense. The DoD would then send the list to the St. Louis Records Center for withdrawal of the records and shipment to Washington where the necessary information on unit assignments would be extracted and added to the computer list of names (12,000). This would complete the data base necessary for the validation steps following. Cost estimated to be at least $75,000 with good unit and time accuracy.

Method 2.--The VA would prepare a letter requesting unit assignments and dates of assignments with an enclosed return-stamped

envelope and dispatch these letters to all 12,000 veterans who have filed claims. As the information is returned it would be added to a computer listing tied to each person's name. The cost would probably be at least $20,000, however, the return rate could not be guaranteed although since these are all concerned veterans having claims it probably would be good. Nonresponders could then be checked out through use of the St. Louis Records Center to provide the missing information. The potential problem with this less expensive method would be that the veterans, in some cases working only from memory, could provide inaccurate unit assignment designations and incorrect dates. There would be no sure way, without using Method 1, to be confident of absolute accuracy.

The author would opt for Method 1 because of the assured accuracy of units and 100 percent reporting on all individuals in the sample.

Assuming one or another way has been used to secure unit assignments and time of assignments for these 12,000 veterans while in Vietnam, we would then undertake two comparisons:

First Comparison: A computer program would be developed to provide a military unit of assignment frequency distribution bar graph from these 12,000 claimants in the VA files. See Tab B for a hypothetical representation of such a bar graph. The Y axis would consist of a listing of all units of assignment as provided by the 12,000 veterans in descending order of frequency of reporting of the same military unit. The X axis would be a numerical scale of the number of claimants. Hopefully, some particular military units would be reflected as having multiple claimants from the same unit. Similarly we could also, on a much smaller scale, prepare unit/individual frequency distribution bar graphs for persons recorded in the: (1) VA Mortality Study, (2) AFIP Tissue Study, and (3) Vietnam veterans in the CDC Birth Defects Study.

The above series of frequency distribution graphs could be used for two possible purposes: First, as a lead pointer to units which might be investigated for unusual herbicide or other chemical/environmental exposures (detailed historical operational review). This might provide better insight into the real disease problems. Second, as a validation technique for the units selected as heavily exposed to herbicides. If our initial selections of units to make up the 12,000 member cohort were reasonably correct as the veterans believe to be the case of exposure, we should find names of claimants who were assigned to these more heavily exposed battalions.

Second Comparison: Similarly the units selected as unexposed to any herbicide spraying from either the ground or air should have no VA register claimants having been assigned. But, if VA claimants did report assignment to these unexposed units (and we are sure of the lack of exposure) this would lend credence to the hypothesis that other substances or environmental factors were responsible for the

reported illnesses. Then the investigatory problems would be much more numerous. Tab C provides a chart representation of the hoped-for positive validation of the sample selected exposed and non-exposed battalion cohorts. If we can achieve such a correlation (as depicted in Tab C) this should provide positive proof to the various veterans organizations that we have selected the proper exposed units for the full scale epidemiological follow-up study.

Standard in-deptn epidemiological techniques would then be employed with the total 36,000 member sample to attempt to prove or disprove altered rates of incidence of suspected illnesses and conditions.

Units serving in Vietnam prior to 1965 were not considered as an adequate population sample for the following reasons:

(a) Insufficient military populations to choose from,

(b) Absence of large quantity orange spraying by fixed wing aircraft or helicopters,

(c) Use of many unstandardized herbicides in small quantities,

(d) Lack of precise data on herbicide spraying,

(e) Variance in combat roles, troop utilization, and weapons employment from those used after 1965, and

(f) Poorly documented Vietnamese unit spraying of herbicides from helicopters using insecticide spray equipment.

I wish to express my appreciation for the thoughts expressed in the letter of 30 October 1981 to the Chairman, AOWG Science Panel from Dr. Michael Gough and Helen Gelband of the Office of Technology which generated the final information necessary for the development of this proposal. Also, without the continuing information input provided by Mr. Richard Christian for the past many months, this proposal would not have been possible. I also appreciate very much the constructive review and critique by Captain Peter A. Flynn, MC, USN.

Respectfully submitted for your consideration.

Jerome G. Bricker

Jerome G. Bricker, Ph.D.
Member, AOWG Science Panel

Enclosures
Tabs A thru C

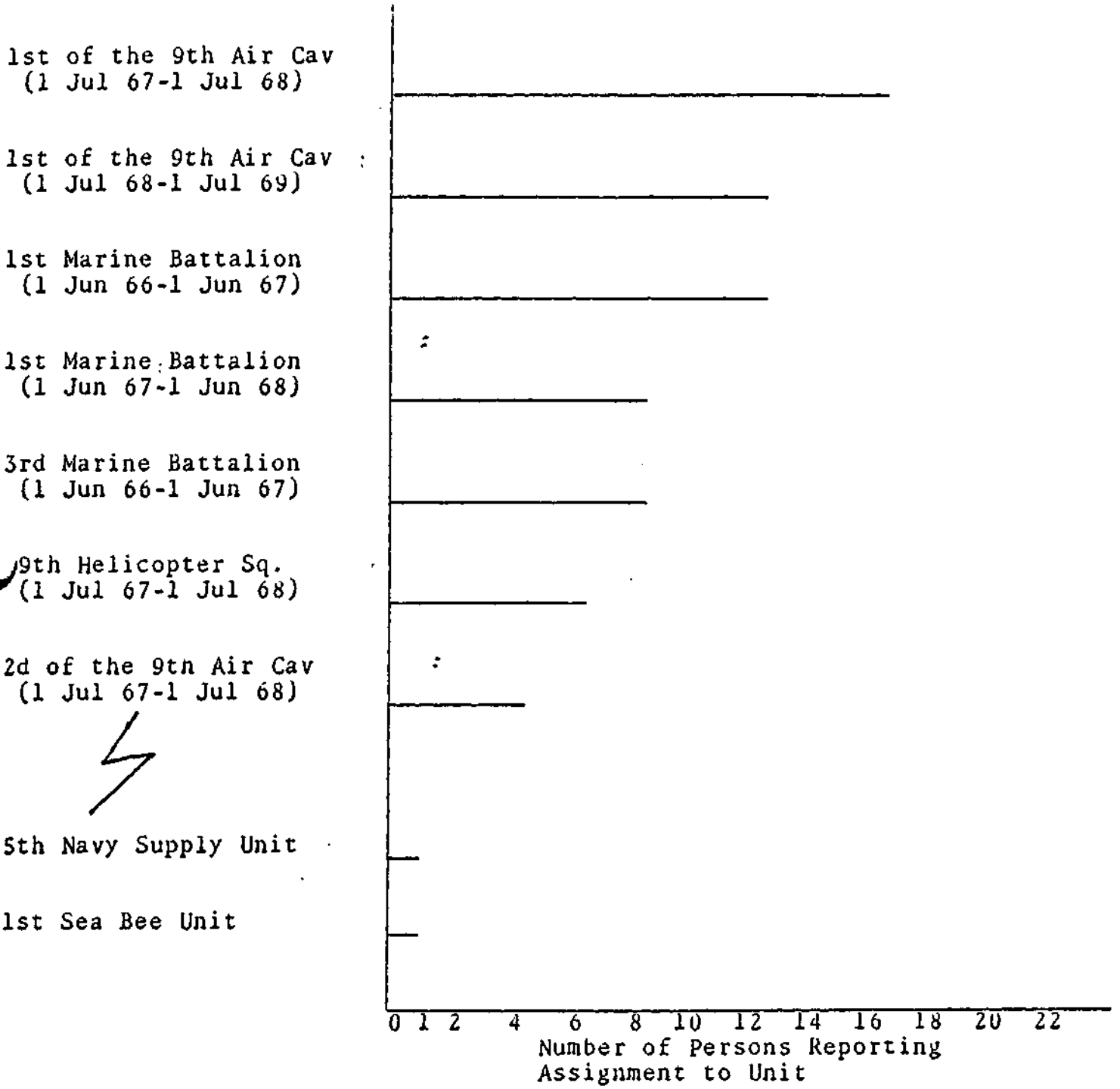
Representation of Highly Exposed Unit Selection Process

Unit Designation	Ranch Hand Exposure (Unit within 1 Km of Spray on following	Perimeter Spraying Done on Units Firebases on:	C-123 Jettisons (Unit within 2 Km of low altitude dump)
1st of the 9th Cav (1 Jan 68-30 Dec 68)	1/5/68 1/10/68 3/5/68 4/10/68 5/15/68 7/10/68	1/10/68 2/28/68 4/15/68 6/1/68 8/15/68	3/5/68
	6 exposures	5 exposures	1 exposure
1st Marine Battalion (1 Jul 67-30 Jun 68)	7/2/67 8/10/67 8/11/67 8/12/67 8/12/67 10/1/67 3/2/68	7/15/67 8/30/67 10/15/67 11/30/67 2/10/68 5/10/68	8/11/67
	7 exposures	6 exposures	1 exposure

Continuing thru the other 8 battalion size units to search a potential sample of 24,000. Then select the 5 most heavily exposed battalions as cohort

(NOTE: All dates above are fictious and are used for illustrative purposes only.)

Unit Assignment Frequency Distribution Chart From 12,000 Veterans Claims



(NOTE: Values are fictious and used for purposes of illustration.)

Validation Sample Technique

Selected High Exposure Units	Claimants found from	
1st of the 9th Cav (1 Jan 68-30 Dec 68)	AOR	12
	VA Mort. Study	2
	AFIP Study	1
	CDC Study	2
1st Marine Battalion (1 Jul 67-30 Jun 68)	AOR	8
	VA Mort. Study	1
	AFIP Study	2
	CDC Study	3

Selected Non-Exposed Vietnam Units		
1st Navy Sea Bee Unit	AOR	0
	VA Mort. Study	0
	AFIP Study	0
	CDC Study	1
10th Tac Recon Ranger Battalion	AOR	0
	VA Mort. Study	1
	AFIP Study	0
	CDC Study	0

(NOTE: Values and units are fictious and used for illustration purposes only)

ORANGE EXPOSED VIETNAM COHORT SELECTION

CATEGORY "A"

1. SELECT BATTALION W/GOOD RECORDS
   - A. GOOD RECORD BATTALIONS
   - B. POOR RECORDS → HOLD IN RESERVE
2. DETERMINE BATTALION OPERATING LOCATION DURING 1 YR WINDOW OF HEAVY SPRAYING
3. COMPARE BATTALION OPERATING LOCATIONS TO RANCH HAND SPRAYING MAPS BY WINDOW YEAR:
   - A. OPERATED IN HEAVY SPRAY AREAS
   - B. OPERATED IN AREAS NOT SPRAYED → SAVE FOR CAT. "B" USE
4. BUMP BATTALION LOCATION MATRIX (UTM/DAY-BY-DAY) AGAINST HERBS TAPE IN COMPUTER
5. ORDER BATTALIONS FROM HIGHEST TO LEAST RANCH HAND EXPOSURES
   - A. HIGHEST EXPOSED BTNS(6-7)
   - B. LOWEST BTNS EXPOSED ↳ SAVE RPTS.
6. REVIEW BTNS FOR PERIMETER SPRAYING AND DOCUMENT DATES
   - A. BTNS WITH MOST FREQ PERIM. SPRAY
   - B. BTNS W/LEAST PERIM ↳ SAVE RPTS
7. COMPARE BTN LOCATIONS TO R.H. DUMP LOCATIONS
   - A. BTNS CLOSE TO DUMP(s)
   - B. BTNS NOT NEAR DUMPS ↳ SAVE RPTS
8. SEARCH BTN. MORNING RPTS, IDENTIFY PERSONNEL EXPOSED
9. RETRIEVE INDIVIDUAL PERSONNEL 201 FILES AND VERIFY ASGMTS
10. PROVIDE INDIVIDUAL LISTS W/EXPOSURES (RH, PERIM, DUMPS) TO VA.

NON-ORANGE EXPOSED VIETNAM COHORT

CATEGORY "B"

1. SELECT BTNS AND OTHER UNITS W/GOOD RECORDS NOT OPERATING IN R.H. SPRAYED AREAS
   ↓
2. DETERMINE UNIT UTM LOCATIONS DURING 1 YEAR WINDOW
   ↓
3. BUMP UNIT LOCATIONS AGAINST HERBS TAPE FOR VERIFICATION
   ↓
   A. UNITS NOT EXPOSED
   ↓
   B. UNITS EXPOSED
      ↳ DISCARD
4. REVIEW UNIT RECORDS FOR PERIM SPRAYING
   ↓
   A. UNITS WITHOUT PERIM. SPRAY
   ↓
   B. UNITS HAVING PERIM SPRAY
      ↳ DISCARD
6. SEARCH UNIT M.R.'s, IDENTIFY ASSIGNED PERSONNEL
   ↓
7. RETRIEVE INDIVIDUAL 201 FILES, VERIFY ASSIGNMENTS AND NO OTHER TOURS
   ↓
8. PREPARE INDIVIDUAL LISTS W/ASGMT INFORMATION FOR NON- EXPOSED COHORT

NON-EXPOSED U.S. COHORT SELECTION

CATEGORY "C"

1. REVIEW POSTS/CAMPS/STATIONS FOR ADSENCE OF HERBICIDE USE
   - A. NO HERB USE
   - B. HERB USE → DISCARD
2. SELECT STABLE UNITS IN REQUIRED TIME WINDOW
3. SELECT UNITS NOT REASSIGNED TO VIETNAM
4. REVIEW MR's FOR ASSIGNED PERSONNEL
5. RETRIEVE INDIVIDUAL 201 FILES TO VERIFY ASGMTS
6. PREPARE LIST OF NON-EXPOSED U.S. COHORT

d. Laboratory Tests pp 51-60

Purpose of the Tests

1. Complement the physical examination

   a. especially for organ systems known to be affected by Agent Orange

   b. assist in the detection of subclinical or impending conditions, not revealed by signs, symptoms or physical examination.

2. Provide a general screening battery for all organ systems for which laboratory tests are useful.

Comment: While the first purpose can be fairly easily defended, the second is really a fishing expedition, comparable to screening a general population for any or all diseases without regard to prevalence. ~~THXNXTHXXEXXXXXXXXX~~ sensitivity and specificity will be quite low.

It is not clear from the statement of purpose whether the laboratory data is to be used primarily to detect disease in identified individuals who may have been exposed to Agent Orange; or if findings will serve to chararterize previously identified exposure and control groups. If the latter is intended, the costs of a fishing expedition may be justified.

Quality Control of Laboratory TEsts

Quality control, including blind split samples, and validation of laboratories are alluded to as being detailed in a quality control section. Assurance of on-going inter-laboratory comparability so that data derived from a number of laboratories can be justifiably pooled, is not a simple procedure. I would recommend that the Standardization Programs used by Clinical Chemistry ~~NXX~~ Division for NHLBI and NHANES studies by used as a tested and proven paradigm.

"Procedures ,,,,,,must be standardized". I agree. But again, all procedures must be standardized, including not only the collection through the mailing of the specimens and the testing of the specimens, but also the clinical procedures of physical examination, recording and interpretation. In addition,

to the requirement for individuals responsible for expediting the handling and shipping of specimens, a single individual at the central laboratory should be designated as responsible for the overall laboratory validity system including all aspects affecting the validity, quality and surveillance system for test results, in the central laboratory as well as in the examination centers.

p 53

The neuromuscular system is included as a recommended organ system for study. I can see no obvious connection between the rationale on p 52 and this inclusion, unless it is suggested that the endocrine systems affect nerve and/or muscle.

HEMATOPOIETIC SCREENING

If RBC indices are to be included, it is, or course, necessary to do red blood cell counts. It would seem somewhat and overkill, as a screening procedure, or as an epidemiologic case control studey to include rbc, hct and hgb; one of these should be sufficient. Sedimentation rate can be easily combined with hct. Prothrombin time is probably not necessary if it is, as I suspect, a liver function test, since (see below) a number of these are proposed.

RETICULOENDOTHELIAL SYSTEM

I would recommend the following tests:

WBC with differential (this can be automated)

T and B cells

Quantitative specific proteins

I believe all of these should be done on all participants, if ~~it~~ subtle alterations in the immune system are suspected.

HEPATIC SCREEN

If the intent is to detect with maximum sensitivity, all differences between a subject group and the control group, or a subject group and so-called normal values, then the more tests the merrier, but also the more costly.

If the cost per adverse finding is to be maximized, then tests which are

persistently abnormal after the initial hepatic insult should be selected.

Gamma glutamyl transpeptidase (GGPT) is elevated in most liver and biliary tract disorders (ie is not specific) is relatively persistent after liver insult compared to other tests (especially in the later stages of recovery after hepatitis). It is a microsomal enzyme induced by alcohol and other drugs (which may be an advantage or disadvantage), GGTP as a xx screening test can replace SGOT and Alkaline phosphatase.

Indocyanine green clearance is a good liver function test xhi which is non-invasive after the iv bolus has be administered. It is non-irritating, non-toxic and is measured by an ear-lobe photometer.

Urine uroporphyrins or blood porphyrins are worth doing, Urine tests usually require a 24 hr urine collection, but a 2 hr timed collection may be satisfactory.

Bilirubin measurements will not be useful in characterizing the non-symptomatic individual but may show up inter-group differences.

It is not clear to me that cholesterol and HDL and triglycerides are part of the organ screen. It is true that Triana studies seemed to reveal some group differences but they have not been related to health or dideases

RENAL SCREEN

Urinalysis needs to be defined. It should include stained sediment examination, protein and rbc especially. Specific proteins sbch as transferrin, B_2 microglobulin and lysozyme may reveal subtle increases in small molecule permeability changes in the glomerulus.

I prefer serum creatinine to BUN, especially in transported specimens. It is more stable and less affected by protein intake and state of hydration. It is somewhat age and weight dependent, but this could be cancelled out by an appropriate case control protocol.

ENDOCRINE SCREEN (presumably for thyroid and adrenal)

Corticol(8 am). As this implies, values vary by time of day. It is probably not possible to anticipate that all specimens with be taken at 8 am. If urine tests (24 hr) are possible, they give beeter information.

FTI (Free thyroxine index)/ There are at least six or seven different such tests, all giving different normals. Essentially they all measure T_4 and in some way TBG (thyroid binding globulin) or its saturation. I recommedd the use of T_4 alone; or T_4 and $_T3$ pt T_4 and specific TBG (if a satisfactory test is available;

Iam leery of patent compliance for fasting plasma glucose; 2 Hr pp glucose is hard to arrange. I suggest the use of $HgbA_{1c}$. We have been carrying out this test for some of our contract studies; in large numbers; good validity; and it is very much less subject ot short term effects and artefacts;

REPRODUCTIVE SYSTEM (males)

I recommend testosterone and luteinizing hormone (LH).

Semen analysis will be difficult in som many ways that I recommend its deletion.

OTHER TESTS

ECG The use of this test is presumably searching for a measure of stress reserve. While the risk ration is 10/1 for symptomatic vs non-symptomatic, and will D?D the groups well, variability between examination centers will be high/

BP . usual problems of standardization

Chest X-ray (AP and Lateral)

Is this worth the cost? To the study or to the Patient? What is the target of the test?(Heart? lungs? Chest Cavity?)

~~MRRXEXEONNHHXIXOH~~

NERVE CONDUCTION

I do not really understand the rationale unless it is a general effect of toxic substances directly on transmission or on the endocrine systems, I have not seen this as a dioxin effect.

SPIROMETRY

Extremely variable with operator technique place to place.

HEIGHT AND WEIGHT

Will these be used for case/control matching?

SUMMARY LISTS ON Pages 58, 59, 60

These tables contain tests not listed in the body of the document. For examples: differential; LH and FSH depending on semen analysis fesults; creatinine;depending on BUN; 24 hr urine free cortisol; depending on 8 am cortisol;SGPT and CPK ; if SGOT is abnormal; alkaline phosphatase; Total Protein and Albumin--then do electrophoresis if abnormal ; VDRL; LH and FSH if testosserone is low;FTI (if low to TSH; if high do T_4) but FTI includes T_4; d-aminolevulinic acid; Band T cells;.

It is not clear whether the participant is ixpected to return 1-4 weeks later after the initial tests are done to allow the consequential tests to be run.

SELECTED SUBJECTS TO BE TESTED

The basis of selection is not stated (random?)

ANA -if clinical evidence of autoimmune disorders or elevated ESR

Hepatitis A or B on history of liver disease or abn liver function tests

Why not on all? save money, time and effort.

Karyotyping--if offspring have gr birth defects (define birth defect?)

Quantitative Immunoglobulin if history of high?frequencey of infectious disease.

I prefer specific serum pooteins on all subjects.

GI series on all positive hemoculs

Drastic; test should be repeated under controlled conditions

These tests (above)sound like suggestions for appropriate clinical care followup of incidental findings.

Comments Pertaining to "Protocol for Epidemiologic Studies of Agent Orange" dated January 22, 1982

1. The following comments are provided with references to paragraphs and page numbers as marked in the upper right corner of the page:

a. Page 1. (Introduction), paragraph 2, last line: Our records show 543,000 personnel serving in Vietnam in 1968.

b. Page 1. (Introduction), paragraph 4, lines 3-5: We disagree that perimeter spraying was minor. In certain areas it was quite frequent and employed considerable amounts of herbicide, often on a scheduled basis.

c. Page 4, last paragraph: Considering the problems we are having with the relationship between the BIRLS file and the DMDC military records file it would seem rather unlikely that the mortality study could be finished before the final data collection instruments have to be designed. It should also be mentioned that the Agent Orange Registry does not contain information on the individual unit assignments and dates of assignment while in Vietnam. It would seem, however, that the frequency distribution of complaints in the Agent Orange Registry might be undertaken if they have been keyed into the tapes.

d. Page 5, 2nd paragraph, line 1: Our records show that the first use of herbicides took place along the road to Kontum using Navy Hidal helicopter spraying on 10 August 1961.

e. Page 7, 1st new paragraph, last line: Agree fully with the caution statement in regard to relating animal effects to human effects, particularly when we consider the 2,500 times greater LD_{50} dose for hamsters compared to Guinea pigs. It is a point which should be emphasized.

f. Page 10, 1st paragraph, mid-page: We suggest he might wish to add chemical detachment personnel who were involved in base camp perimeter spraying as personnel who may have high exposure to herbicides. So far, we have not found any particularly high exposures in Engineer units. Engineer units could have had high exposure opportunities if they were involved in major spill clean-up operations such as the leak at Bien Hoa (7,500 gallons). We have not located the unit that was involved in this clean-up and repair of the delivery pipes.

g. Page 11, line 3 from top: The difficulty in using the records lies in the fact that very experienced records management personnel are necessary to piece together the exposure picture with respect to time and place. There was no reason evident at the time which would make it necessary to record exposures to herbicides.

h. Page 19, 1st three lines: We agree completely for the need to have such experts on the staff of the contractor.

i. Page 20, 1st paragraph, 5th line: We consider the time span of 1965 to 1971 as too wide. In 1965-66 period there was not a massive spraying effort and by 1971 most of the spraying had ceased. We suggest a maximum time span of 1967 through 1969 as the highest usage.

j. Page 20, 1st paragraph, line 8: We believe it would be advantageous to include some less serious battle casualties, re-enlistees, officers and multiple tour regular army enlistees. The officers in the companies would likely be exposed to herbicides as were their men. Similarly multiple tour personnel might provide us with a much higher exposed group than single tour personnel.

k. Page 23, 1st new paragraph, line 14: The records would only be considered disorganized from the standpoint of an epidemiology study, they are in an organized structure according to Army records retirement guidance. These types of records were never expected to be used as a basis for an epidemiologic study. Rather, to be useful, the records must be sorted, reorganized, and then extracted for the necessary information. We believe the security clearance problem has been overstated, as many, if not all, of the required records can be downgraded to unclassified or interim security clearances can be obtained for the necessary contractor personnel. It does, however, require pre-planning to have these clearances granted in time to review the small number of remaining classified documents.

l. Page 24, Second paragraph (Step 1): This step infers that one would document all of these various modes of exposure for all times and all places in Vietnam as a first step. If our interpretation is correct this would be very wasteful, expensive, and exceptionally time consuming. The author does not yet understand how and what has to be done to locate the time and place of each one of the exposures, nor could we place boundary limits to the area of contamination or concentration gradients of the herbicide released. The only computerized documentation in existence is for the fixed-wing Ranch Hand missions and for about 5 percent of all of the helicopter missions. All of the other types of exposures would have to be found by very extensive manual record searches. This step should come much further down in the cohort selection process so we would not waste manhours of search.

m. Page 24, Third paragraph (Step 2): This step focuses too early on the location of Company headquarters. We believe that it is more economical to select battalions who were operating in very heavily sprayed Ranch Hand areas by use of the yearly province spray maps already available for both defoliation and crop destruction missions as produced by the National Academy of Science in 1974. Later in the analysis process we do a finer focus on company operations by UTM coordinates on each day throughout the selected time period. Also a company headquarters location does not always effectively locate the operating areas of the combat platoons, especially in air mobile units which can range far and wide.

n. Page 24, Fourth paragraph (Step 3): This is close to what is feasible, however, we would, as stated earlier, establish daily UTM coordinate locations for the cohort company and its subsidiary units and then compare these locations to the HERBS Tape using the computer to get time-distance proximity printouts on which to base the likelihood of exposure to Ranch Hand spray missions. Then the individual Ranch Hand matched companies should have their unit records manually searched in great detail to establish instances of exposure of the company units to perimeter spraying at base camps and firebases from which the units deploy for combat. Finally, the same company units based on their previously recorded daily operating UTM coordinates will be compared to any herbicide dumps in close proximity (2km within 2 days or less post dump). In this last comparison we would work from date-to-date plus 2 days to fix the UTM coordinate proximity. Units meeting these criteria would be input to the computer for later personnel assignment matching (daily assignment locations).

o. Page 25, Step 4 and 5: This is a morning report search. However, some of the members may be absent for various periods of time due to many reasons ranging from combat wounds to detached assignments. Time profiles would have to be made for each man for the entire military unit "time window" (expected to be 1 year, no less than 9 months). Since the exposure date intervals for the unit would be many times less than the whole combat time window (perhaps 20 days compared to 365 days), the individual's presence in the unit should be made by computer comparison to these exposure dates rather than the other way. Day fits to exposure would then be tabulated and reported by classes of exposure, thus:

		Exposures		Time
	R.H.	Perim	Abort dumps	Interval
John J. Jones	7	4	1	670630-680701

p. Page 25, Step 6: This could be done, however, how does one determine if one perimeter spraying is more or less dangerous to the health of the individual than being under a Ranch Hand spray mission. Next, is being close (1km) to a large abort dump more hazardous than either of the former types of exposures? We would rather find an entire troop population that was never (with reasonable certainty) exposed to any of these types of herbicide exposures to be the other end of the dichotomous cohort. We believe this would do as Dr. Spivey wants, namely maximize the differences in exposure between the two cohorts.

q. Page 25, last paragraph: There is no major difference as just as we did in the battalion studies earlier accomplished, we verified individual exposures by the review of 2,400 names for the usual 970 member battalion. Their dates of presence in the unit were verified in relation to spray run proximity by being present for duty on those dates. Perhaps it was so routine in our concept that we neglected to stress this individual location-to-date match-up. Otherwise if we did not do these comparisons, the probability of

exposures and number of exposures could not be made on a man by man basis. Person listing including either SSNs or serial numbers, with frequencies of exposure by class of exposure (as shown in o. above) has to be generated for the epidemiologists to use in tracking down the subjects of the study assigned to the various cohorts.

r. Page 26, Section on Documentation of Agent Orange Use: We completely disagree with this method of approach as it is unnecessary and would be very costly and time consuming to do all instances of exposure. MACV records are not the key. Rather the HERBS tape maps can be used to save much time in locating potentially heavily exposed units. After locating units having operating UTM coordinates right in these very heavy spray areas bump these daily UTM coordinates against the HERBS tape on the computer and then after multiple exposures are obtained dive directly into unit firebase records to locate perimeter spraying instances and dates. A further complication in looking at the massive MACV records comes from the way they are organized which includes 22 staff elements, plus records sets on provinces, divisions, districts, and MAT team records. We very much agree with the last sentence on page 27.

s. Page 28, paragraph on troop movements, line 8: In some cases this is true, in others it is not. It may not be true for air mobile units in which the company command post might be at a firebase and some of its platoons would be air lifted by helicopter into a landing zone several kilometers from the firebase. Also the company command post may not be synonomous with the company headquarters location.

t. Page 28, Company Likelihood of Exposure: We disagree with the approach to lay out squares of 10 km on a side and record all exposures of Orange in that area as it would involve months and months of effort and be very costly. This would only be useful if we had to do battalion studies on all 333 combat battalions operating in Vietnam from 1961 through the end of 1970. He points out on page 30 one very serious source of error in such a map projection technique and that is you would assume that the Agent Orange persists in the environment. Earlier he said that TCDD has a half-life of a matter of hours. We would be way off the track if we used this methodology to compare exposed units.

u. Page 30, last paragraph: We agree with this paragraph except that we would use the company combat operating location as opposed to the UTM for the company headquarters and would refine the locations to 0.5 km, 1.0 km, and 2.0 km, for periods of same day, 1 day, 2 days, and 7 days post exposure from a Ranch Hand spray track.

v. Page 31, 1st paragraph: We concur in the last sentence as it does imply greater accuracy than is warranted considering drift factors from the spray track and intersection points on the spray line to operating locations of the moving combat company.

w. Page 31, 2nd paragraph: This approach would be a refinement technique and would be useful if we were using Ranch Hand exposures as the most important means of exposure of ground troops. It would require a new computer program development to match exact swath paths by originating and terminating UTM spray coordinates by subsequent dates. However, the problem is not quite that simple. Subsequent spray missions over the same area six to eight weeks later might originate from a point 180 degrees from the original flight path or criss-cross the original spray paths at 90 degrees, or subsequent spray tracks could differ by a few degrees (10 to 20) just because of pilot error or the pilots desire to always start the spray run from out of the sun to make it harder for the ground gunners to sight on the aircraft as it came in to spray. The computer program would therefore be very involved if all of these operational possibilities had to be included. We also understand that when the pilots encountered a source of intense ground fire there was a natural human tendency to turn away from these hot spots so the spray track would be curved and not exactly straight as is necessary in the classic bomb run mode.

x. Page 32, line 11: We assumed that the period of observation would probably be 12 months not 1 week. You would have to look forward and back at least six months in the morning reports to make sure the person was present for duty in the unit. The one year observation period is more complicated as you then may have gaps in his service with his company and to be accurate these must be kept track of in relation to the dates of spraying exposures from any ground or air source.

y. Page 33, 1st paragraph: We agree, he is right on target, and this would generate the lists to be provided to the epidemiologists for the survey plus adding any other necessary personnel data from the individual "201" file folders.

z. Page 33, last paragraph: We agree as to selecting those persons with the maximum and minimum possible exposures considering all of the many other factors and possible error sources from the use of combat records which were never designed to record herbicide exposures.

aa. Page 34, last two lines continuing to page 35: We disagree that the coordinating center should establish the cut points after all of the work has been undertaken. We believe that the cohorts should be defined first and that the Army and Marine staff should initially proceed to find either heavily exposed or presumably (from available records) the non-exposed cohorts as they go into battalion and company records. The method proposed would possibly end up with unequal cohorts especially in the group which is considered to be non-exposed. Finding and verifying unexposed personnel for a period of 1 year in Vietnam we believe will be the most difficult aspect of developing the necessary cohorts. A great deal of manual records search will be required to determine these persons.

bb. Page 35, 1st paragraph: Such computer maps in the form of plastic overlays were developed for each year of the HERBS tape records for both

defoliation (1 set) and for crop destruction missions (another set). These very well define the provinces where heavy spraying was accomplished. We took advantage of these to select the original battalions used in the battalion studies which were provided to Dr. Spivey. That is why we had so many units operating close to Ranch Hand spray tracks on several occasions. We have already done what he proposes early last year in completing our test runs submitted to the Science Panel.

cc. Page 36, item A: These are already available in map form by years as discussed above.

dd. Page 36, between items A and B: He has left out a critical step which could wreck the whole study and that is we must select battalions (including their assigned companies) which have good and complete records or down the line in the search process we would run into disaster and have to start over looking for other battalions. We cannot afford to search battalions if there are serious gaps in the records during the one year time window.

ee. Page 37, line 17: The heavily forested areas are in the north, the Delta is flat with marginal swamps and rice paddies.

ff. Page 38, last paragraph: We do not maintain socio-economic data in the personnel folders nor any background on the soldier's family or their economic status. Limited educational information can be obtained but is this necessary? By limiting the cohorts to draftees only you will limit the number of available personnel significantly. We do not agree with this limitation. We wished he had explained what is meant by major differences between individuals in noncombat and combat units.

gg. Page 39: We disagree on excluding regular Army personnel and officers. Many such personnel were in the thick of combat and were exposed as highly as any of the draftees. We thought the objective was to find out what if any effects Agent Orange had on ALL of our personnel who fought in Vietnam. It is true that many of the regular Army personnel, both officers and enlisted personnel, were much older than the average draftee, and hence they might have a different susceptibility to herbicide effects which could have become apparent before those of the younger draftees. Also multiple tours in Vietnam could provide for longer exposure periods to herbicides and even to higher exposure concentrations of dioxin if they served over there beginning in 1961 and later when the dioxin concentrations may have been higher in very localized areas. In the fourth line from the bottom of the paragraph we cannot say it is impossible until we review records of personnel in the non-exposed cohort. This could be very dependent upon the individual's military occupational specialty.

hh. Page 40, 1st paragraph: The tour in Vietnam was 12 months and they were most careful to rotate them out on time and the draftees were in for two years, not three.

ii. Page 41, 1st paragraph: The Army Agent Orange Task Force has now located 1,406 women who served in Vietnam. There were 518 enlisted WACs, 91 officer WACs, 743 Army Nurse Corps Officers, and 54 women in the Medical Service Corps. The women, however, were not in front line combat units. Shortly we expect to have a name, serial number, unit of assignment computer print-out of these ladies.

jj. Page 44, 1st paragraph: We fully support the need and advisability of maintaining the strictist secrecy of the lists of personnel considered to have been exposed and those who were non-exposed as generated by the records search.

kk. Page 47, last paragraph: From the detailed nature of the questions covered in the questionnaire, we seriously doubt the recall capability of the subjects after a period of 14 to 15 or more years. Perhaps in some cases they may be able to draw on copies of their military records if they retained them. Such recalled information would seem to be suspect as to exact times and places. We have also found that some service members relate nicknames which cannot be found as recognized and recorded locations or firebases.

ll. Page 48, 1st paragraph, line 8, Sentence starting with "For instance,...": This may not be valid evidence unless actual defoliation effects are recorded. We have found instances in letters from veterans where insecticide spraying C-123s were believed to have sprayed personnel with herbicides when it was not true. Similarly, helicopters were used for malarial control operations using insecticides not herbicides. The insecticide spraying C-123s were shiny aluminum ("Silver Birds") as the insecticides destroyed and removed the camouflage paint. Likewise, aircraft off in the distance in silhouette often cannot be identified as to whether they are painted in camouflage or are shiny aluminum. Memories over 15 years also become vague and lack such specific details.

mm. Veterans questionnaire: References are to pages of Questionnaire section:

(1) Page 2b, after question 6: Why not ask if he or she was drafted? Also, if you ask when he entered the service, why not then immediately ask when he left the military?

(2) Page 4b, Instructions block in center: If father is deceased, why not ask for cause of death and date of death at this point in the questionnaire, not later and much further into the questioning?

(3) Page 5b, Instruction block in center: If deceased, why not ask for cause of death and date of death?

(4) Page 8b, Card 18: Ignores possible exposures of electrical workers (linemen) to PCB containing transformers and exposure of other service type workers such as those involved in the transport industry (railroads,

trucking) to leaking toxic substances during shipment. The authors probably have never walked through a railyard and seen evidence of leaking chemicals in those yards, e.g., piles of powder. Firemen are also often exposed to toxic chemicals while fighting industrial fires. This chart needs to be expanded and more thought needs to be devoted to the subject. It is incomplete. The CDC Birth Defects Questionnaire is much better in format and questions on chemical associations.

(5) Page 10b, Question 19b: Why not present another card with a list of dangerous agricultural chemicals to aid in recall?

(6) Page 12b, Hobby Questions: Card 18 falls short in covering hazards from hobbies which can cumulatively give the person high exposures to dangerous substances, e.g., lead vapors from hand-loading of ammunition; lacquers and other organic substances from furniture refinishing; glues (organic) from model building, formaldehyde from taxidermy and the list goes on and on. Needs more thought.

(7) Page 23b, Question 35c, Page 24b, Question 36: Would seem unlikely without going through past records that the average person could answer these questions with any degree of accuracy, especially as to name of the physician say 20 years ago.

(8) Pages 34b-38b: Doubt if you will get any factual answers, you are almost asking for self-incrimination because these questions are being asked by an interviewer and it is part of a questionnaire with the person's name on it and all other identifying information. It may terminate the interview in a flash when these questions are asked.

(9) Page 42b, items h. through l: Even a trained medical person may not know these conditions. It is absolutely impossible and wrong to ask the average former GI if he had these by using medical terminology given by an interviewer who may not be able to describe the disease or condition in layman's terms.

(10) Page 45b, Question 80: Do all people know how jaundice affects skin color? We doubt it.

(11) Page 63, items h. and i: Medical terminology will not be understood.

(12) Page 72b, Question 122, c. and d: Do we expect laymen to be familiar with laparoscopy and endoscopy? Will interviewer be able to explain procedure?

(13) Page 80b, Question 129b and c: Will an average person be able to differentiate between a intravenous pyelogram and a retrograde pyelogram? We doubt it.

(14) Page 84b, Question 132, a through w: This is foolish to expect an average person to know all of these diseases. Many won't know what you are talking about. We bet many nurses couldn't define this list, let alone someone who may not have finished high school. The very same comment applies to the list on page 88b. It is naive to ask questions like this and expect to get accurate answers.

(15) Page 93b: Will the average person know what an EEG or an EMG is by the initials? I doubt it. Visit some parts of rural Appalachia and run this questionnaire and see what you get in the way of answers. Most people have had no medical training. Same comments apply to page 96b, 98b, 100b, 102b, 104b, and 106b.

(16) Page 132b, Question 156a through l: Same concern for use of medical terms that will be unknown to interviewee and interviewer such as scleroderma and Pagets disease.

(17) Page 142b, Question 164D: Very little likelihood anyone will know the actual herbicide name used unless he loaded from the drums with colored bands.

(18) Page 145b, Question 167A-C: From these questions the person would almost have to be a walking computer or have kept a daily log which focused on herbicides. Spraying operations could also include insecticide spraying against mosquitos.

(19) Page 146b, Question 168, A-E: Does this question apply to the entire life of the person or just his military service?

(20) Page 147b, Question 169C: How can the individual answer such a question when the best scientists in the country can't come up with what constitutes an exposure? A useless question.

(21) Page 150b: Could not find any place in the questionnaire where we asked for the former military member's service serial number except for perhaps in this release form where they incorrectly ask for "Service Record #."

(22) Page 173b, Questions 30-37: Very few women smoke pipes or cigars on a regular basis. Are all those questions necessary, were they just copied from the male questionnaire? A large number of good questions could be retrieved from the CDC Birth Defects Questionnaire which is of very high quality.

nn. Physical Examination: References are to the pages in physical examination section:

(1) Pages 53-55: All testing appears to be directed just to finding effects of herbicides on various organ systems. This is not enough if we wish to find out what is wrong with the individual. The laboratory procedures

should include testing for latent bacterial and parasitic diseases which could be producing the symptoms experienced by the concerned veterans. The exam sequence should check for bacterial, viral, fungal, and parasitic diseases. We owe it to these men to help find out the source of any problems they may be experiencing.

oo. Confounding Factors Section, Page 64: This is a great deal of information to extract from the service and medical records and in some cases it is rather inexact in description. Some bits of information may be lacking as a result of records purging at time of discharge. It may take several hours to extract such data especially from the medical files which may be handwritten. The retrieval of all of this information on thousands of subjects before they are located and participate in the survey would be very expensive and perhaps wasteful. No mention is made of any interest in military courts martial convictions or records of disciplinary actions and/or records of illicit drug abuse while in the service, or recrods of latent diseases found when they departed Vietnam. We are finding some of this data.

pp. Suggested Initial Contact Letter, Page 74: Part of the first sentence of the letter has been left out. The whole thrust of the first paragraph is wrong. It should not include the word "compensation." We could not get favorable Presidential signature for Ranch Hand letters, not likely you would get it here without considerable effort. In the last paragraph on Page 75 the letter gives an assurance which may not be possible especially if a serious disease or condition is found in a commercial or military pilot that could be a serious hazard to the public. We, as the Governmental investigators, would have a legal and moral obligation to make the necessary flight safety notifications. The same could also apply to other critical jobs having to do with public safety or health as to diseases present.

qq. Page 79, 1st paragraph: We suggest that Department of Army and Marine Corps records staff members are already fully trained and highly competent to perform these described types of abstracting of data from the individual 201 record jackets.

rr. Pages 83 and 84: Many subjects could have been treated by several physicians. The authors recommend questionnaires be sent to each of these physicians on these subjects. Do you think these physicians will fill out these questionnaires for nothing?

ss. Page 91, subparagraph a: We disagree that the other forms of spraying and accidents need to be computerized in mass for all of the country. It is not necessary or desirable and would take months of extra time and waste lots of money. They do not understand either the problem or the state of the military records and how difficult it would be to place all of these locations. Ground spraying for all unit locations would probably exceed the entire HERBS tape record set.

tt. Page 92, paragraph b: A very involved process for all members of the selected companies. If the personnel were dropped before exposures why keep them in file? KIAs and MIAs should be off-loaded to a separate file. We advocate keeping interval information on assigned personnel but only those who are going to be future study subjects.

uu. Page 93, 2nd paragraph: This file is not necessary if we did the job right and included the necessary information called for on page 92.

vv. Page 120, 2nd paragraph: We would suggest a minimum of 1,000 names from each of the two or three sample cohorts be provided to the study managers on which to start the tracing of individuals. This would approximate six battalions after losses are taken into consideration.

ww. Page 124, 1st paragraph, a and b: Believe the exposure likelihood index has been developed so the first 12 month period is saved. However, for a 36,000 member cohort of three 12,000 member subgroups it will take a total period of 18 months. But output lists of say a thousand persons from each of the cohorts could probably be generated within six months of full records search manning requirements and the provision of the necessary computer financial support and priority to do the job. Thus, a time compression to get started could be made of 12 months saving in steps a. and b. It seems step c. accomplishment in 3 months is rather optimistic considering tracing steps and problems usually encountered in interview techniques and physical examinations standardization.

xx. Page 125: No mention can be found as to what should be done in the way of future studies if more diseases and serious conditions are found in those persons who served in Vietnam but were not exposed to Herbicide Orange, or if the illness rates for both Vietnam cohorts were the same but considerably worse than non-Vietnam serving military members.

yy. Glossary: The following comments are made concerning the words or phrases listed:

(1) Antipersonnel gas: This is a strange definition for a war gas. War gases are usually defined as either "persistent," e.g., VX or "non-persistent," e.g., GA, GB. Or they be classified as "lethal," e.g., GB, VX, Phosogene; "incapacitating," e.g., BZ; and "riot control" such as CS, CN, and DM. Tear gases are antipersonnel, as are almost all gases but are more correctly known as "riot control agents" since they are considered non-lethal.

(2) Battalion: Consists of four letter companies and a Headquarters and Headquarters Company. The heavy weapons are in the fourth Company. The four companies are not stationed within range of the hardest hitting weapons, rather sections of the "weapons company" are assigned as the current battalion mission dictates.

(3) Cocodylic acid: Add "pentavalent" before "arsenic."

(4) Company: An organized unit of a combat battalion. Combat support companies may vary in size and mission.

(5) Company Morning Reports: Should include that they show the presence for duty of military personnel in the unit and absences of personnel from the unit.

(6) Suggest addition of: USARV: The U.S. Army in Vietnam.

(7) UTM: These grid coordinates are not used exclusively by the military.

Reviewer "C"

Date February 23, 1982

From Science Panel Members

Subject Review of Proposed Study of Vietnam Veterans

To Chairman, Agent Orange Science Panel

In anticipation of the meeting scheduled for February 24, 1982 to discuss the study protocol we are writing to outline briefly areas which should receive consideration in discussion.

It is evident from the protocol that the contractors have benefited from additional information on the uses of Herbicide Orange in Vietnam. Their proposed "exposure likelihood index" follows conceptually the Science Panel's earlier statements that exposure will have to be defined on a probability basis by unit of service. It will be important to explore in detail the interface between the proposed plan for establishing the index, and current plans of the DOD to continue refining exposure data. The contractors propose estimating an index for each individual. This plan merits further discussion with the DOD to assess feasibility and relative degree of accuracy. Additionally, the question of whether it would be possible and useful to estimate degree of exposure to other herbicides in Vietnam as descriptive data for the cohorts and as further definition of other service exposures should be explored.

Overall, the study as proposed is extremely large, and attention should be given to the practical problems of conducting a study of this magnitude. The contractors do outline an administrative system for the study, but other factors such as compliance may be a problem. The questionnaire is extremely long and cumbersome and administration of this battery plus extensive physical exams for a proposed total of 12,000 is a formidable task.

Hopefully, the proposed pilot test of the questionnaire and physical exams will result in some streamlining of the test instruments. The questionnaire should be condensed with consideration given to refining endpoints for analyses. While the contractors do suggest a plan for data analyses, it is very possible that if all data collected are analyzed, there will be positive associations which are not meaningful and difficult to explain. It also would be helpful to see a copy of the Australian veterans' questionnaire in order to evaluate additions and modifications made by the contractor. Finally, consideration should be given to the accuracy of the answers which will be received in response to questions on illegal drug use.

The contractors suggest a review panel to oversee the conduct of the study. We feel that this idea should be endorsed, with the panel consisting at least in part of non-government scientists.

Overall, the protocol has developed and become more specific since the draft which circulated earlier. The question at this time is whether the proposed study is feasible given its size, and whether meaningful answers will result. The pilot study is a key element which must be used to refine the proposed plan.

Reviewer "D"

Date February 11, 1982

From

Subject Comments on the Proposed Protocol for the VA Epidemiology Study

To Dr. Vernon Houk
Chairman, Science Panel of the
Agent Orange Working Group

In general, the proposal is well thought out and gives sufficient detail. It is very comprehensive and well written. However, I have some very specific concerns.

On page 23-37, exposure and means of determining exposure are outlined in great detail. This process is very cumbersome, time consuming, and expensive. The data base used for this information is at best incomplete. Even if it can be assumed that information on length of stay in sprayed versus nonsprayed areas can be accomplished, this will give no information about dose. In addition, in a given population response to a given dose varies. To collect exposure data in such great detail seems to be an exercise in futility. Troops that have had high exposure should be identified and used as the exposed group. If the turnover, R and R leave, hospitalization, temporary duties, etc., follow a relatively consistent pattern, then it would be unnecessary to collect this information. Hospitalization information could be obtained from the veterans and verified on a subsample.

The rationale for excluding officers and "multiple tour" individuals is not reasonable. Information on tour of duty could be obtained from the veterans, simply coded, and regression analysis could be done. What will be done with military who served in Vietnam and South East Asia (not Vietnam)?

Page 22 Why follow the entire cohort? Would a prospective mortality study suffice?

Page 23 I think the development of an exposure gradient will be based more on fiction than on fact.

Page 55 It would be sufficient to have EKGs on patients over 40. What are the benefits of chest X-rays, routine spirometry, and nerve conduction tests? Blood pressure measurement should be standardized.

Page 59 Liver function tests. γ-glutamyl-transpeptidase is more sensitive than SGPT. What is the rationale for doing SGOT as a screen rather than SGPT? What is the reason for doing a CPK or alkaline phosphatase? Since myalgias are part of the list of complaints, should a CPK not be done anyway?
What are the urine porphyrins? What are the criteria for abnormal sperm?

Page 64 It should be determined whether it would be cheaper to first get the serviceman's name and social security number; then an attempt to locate him should be made. Detailed information should only be obtained on those that cannot be located the first time around. I think the veterans' organizations should be contacted for their input into locating veterans, and veterans should be located through them first.

Page 74 The first sentence is unintelligible.

Page 84 ..."questionnaire to be filled in by personal physician"... The response rate may be very low. However, this may not be a problem if this is merely a check on what kind of biases are introduced. How will a discrepancy between the reporting personal physician and the examining physician be treated?

Page 86 The laboratory used for validation should be involved in the design of the collection and shipping of samples. It should inspect the participating laboratories and should assure that the performance of the laboratories is consistent over long periods of time. This process should be started as soon as possible and should be in place before samples are taken.

Page 100 What will be done about missing values?

It also needs to be established how the results of the laboratory data will be analyzed. What will be used as normal range for SGOT for instance? What will be done if differences in SGOT levels between cohorts are found that are within the normal or slightly above the perceived normal range in the general population?

Page 115 An individual in charge of lab and an individual for public relations should be added.

Page 118 Follow-up. It should be specified at what point no further diagnostic work, follow-up, etc., will be done. Who will pay for follow-up, referrals, etc. Pilot testing should be on a 5% sample; for 12,000, this is 600.

The time table is not clear to me.

17C Why is severe acne on the summary sheet, and not chloracne? The physicians need to be trained to recognize chloracne.

The outlined examination for the veterans appears to be very long. It should be estimated what the total time is that the veteran has to spend on this endeavor. An appeal may have to be made to employers not to charge veterans with leave for this.

Questionnaire

The questionnaire is much too long and should be reduced to at least one-third of its present length. By collecting a vast amount of information, the investigators will be diluting their efforts to the point that the study will become unmanageable. Furthermore, cooperation of the participants will drop off rapidly. It is very important to determine the amount of time the veteran would have to spend on the entire study.

draftees, etc. as described on top of page 39) as their attitudes might be quite different. Consistency in results would be evidence against bias. To exclude regulars or others depends for its rationale on expected differences in exposure or susceptibility to the diseases in question.

8. The questionnaire is an extensive fishing expedition. There are way too many questions! Spurious positive results are likely, and the questionnaire should be shortened and focused on a priori hypotheses. Perhaps questions should be included where no exposed vs. non-exposed differences would be expected, as a check on validity. Will there be verification against hospital or other records?

9. The physical and neurological exams are also far too subjective and extensive. How will they ever be analyzed? If any are to be included, they should be selected, limited tests with specified criteria for examination and for interpretation.

10. Ditto for the laboratory tests. How will they be interpreted? Do the tests noted measure effects from an exposure many years before? I doubt it. Happily, chromosome tests aren't mentioned (unless I missed it).

11. The UCLA Survey Research Manual is standard and okay. If a telephone survey rather than mail survey is decided upon, we have found it cheaper and better to have bids from telephone survey groups such as the Gallup or Harris Poll organizations. The latter tend to collect all of the data within a few weeks to months. University survey research groups stretch data collection over years, increasing the possibility of public controversy, the news media, or veterans' groups influencing results.

12. The plan for analysis merely states general approaches. Sorely needed is a statement about how every data entry item will be used in analysis. Dummy tables for the analytic plan would be helpful. This might make it obvious that vast amounts of the data proposed to be collected would be useless.

13. No budget is provided. This might be a hidden plan to make up the deficit from California's Proposition 13 (limiting property taxes).

Recommendation

I recommend against the proposed study. Several studies of explicit a priori hypotheses and/or selected subgroups of this population are preferable. A case control study (based on mortality, VA admissions, and a mailed questionnaire with selected validation) or a much more limited and defined historical cohort study of the entire group might be considered.

I recommend against proceeding with the study as described. It is diffuse, and may lead to confusion or even spurious positive results.

Reviewer "F"

February 23, 1982

CONFIDENTIAL

SUBJECT: Review of Proposed Protocol - VA Epidemiology Study

TO: Vernon Houk
Science Panel
AOWG

As requested, I have reviewed the subject protocol. The document has not left my office, nor has it been discussed with anyone. In the previous review, I only felt qualified to comment on the exposure portion of the study. The same applies in the current draft.

My major objection to the previous draft was the exposure section. I am pleased to see the authors have addressed this section in somewhat greater detail in the current draft. The establishment of an exposure likelihood index has merit considering we will never be able to unequivocally establish exposure by more classical methods. Currently we are chemically analyzing urine and patch samples to determine exposure on a quantitative basis for a number of the phenoxy class of herbicides.

In regard to the proposed exposure likelihood index, two major questions arise, i.e.:

1) If we are able to get all of the information required to formulate an exposure likelihood index, would any conclusions based on these estimates be scientifically valid? If the answer is "no", then we can proceed no further with the epidemiology study. If the answer is "yes", then we would need to proceed to the next question, i.e.:

2) How much valid information could we get on the six steps needed to establish such an index? The answer to this question clearly lies with Mr. Richard Christian, Department of the Army.

If we are unable to get fairly precise numbers for each of the steps, then the index is further weakened. A decision would have to be made then at what point the index loses sufficient accuracy to become a useful tool for estimating exposure.

I recommend Mr. Christian be asked to supply the Science Panel with his best estimate of obtaining the necessary information. More specifically, I

recommend he provide us with a fairly detailed estimate of time, costs, and chance of success for developing this information. When this is complete, then we can make a decision as to how to best proceed with this study.

Reviewer "G"

Date February 19, 1982

From

Subject Scientific review of Protocol for the VA Epidemiology Study of Ground Troops exposed to Agent Orange

To Vernon Houk, M.D., Chair, Science Panel, AOWG

This is an excellent and comprehensive protocol for an historical cohort study in which it is proposed to compare health status of veterans with high and low likelihood of exposure to Agent Orange in Vietnam. It is proposed to evaluate health status of individual veterans via a comprehensive examination including questionnaire, physical examination, clinical laboratory tests and psychological evaluation. It is proposed to determine exposure status via military assignment to armed forces units operating in Vietnam during the period 1965-1971 in situations involving high and low exposure to Agent Orange as determined by review of Department of Defense records of troop movements and herbicide dispersion. There are several elements in the protocol which should help to detect, minimize or avoid bias due to missclassification and selection of respondents' health and exposure status. In addition, it is proposed that a pilot study be conducted to estimate participation rates, to refine the instruments used to measure health status, and to test the feasibility of the method for determining exposure status.

There are several suggestions, however, which may be useful additions to the protocol before it is adopted or even processed further. These are presented below according to the issue addressed.

Questionnaire:

I would suggest that a section on LSD use be included among the items on drug use. This is based on possible concern for chromosome breaks and other genetic damage due to excessive use of this drug. I would also suggest that the use of coffee be included among items on the spouse's questionnaire because of possible association with birth defects.

Exposure Cohorts:

I would suggest that two additional cohorts be included in the study population, although this will probably necessitate an even larger group to be identified and examined.

1) A non-Vietnam Veteran Cohort should be included in order to assess the overall effect of service in Vietnam.

2) A cohort of Vietnam Veterans with identifiable, but minimal exposure to Agent Orange should be included. This would necessitate re-defining the proposed low index-of-exposure group to one with no known exposure and a high likelihood of no exposure to herbicide Orange as has been suggested in Dr. Bricker's memorandum. The advantage of the intermediate cohort is that this is what many veterans consider to be an exposure and thus should be more satisfying to Veterans' needs to be apprised of health effects to be expected from this type of exposure. From a scientific standpoint, this should provide for an assessment of dose-response estimates which lends considerable power to interpretation of cause and effect relationships.

Participation rates:

The expected participation rates seem a little high--both the follow-up and "volunteer to participate" phases. While I agree that the level of participation can and should be useful in making decisions regarding possible bias, they may be overly optimistic. Perhaps a more detailed discussion should be developed as to how best to evaluate specific levels of participation. The figures included in the protocol (page 123) are not adequately justified.

Cost:

While cost should not be of concern during scientific review of the protocol, some recognition should be given to the very large commitment of resources that a study of this size and scope entails. This will certainly be a major factor when the proposed study proceeds toward implementation and the various agencies' responsibilities must be considered.

In summary, the protocol seems well designed to measure the association between adverse health effects and estimated exposure to Agent Orange among Vietnam Veterans in so far as this can be estimated from existing records. A few suggestions included in this review may help to focus the Agent Orange issue and to broaden the scope of the study to include the possible adverse health effects associated with the Vietnam experience.

Reviewer "H"

Date February 16, 1982

Subject Questionnaire Review

To Acting Director, Center for Environmental Health

I have reviewed the V.A. draft Veterans questionnaire. This was accomplished without access to the study protocol. Therefore, some of the following suggestions may have already been covered in the protocol itself. It is not the intent of this brief review to delve deeply into very specific problems of format and layout of the instrument. These issues are relevant, however, to this questionnaire and would perhaps require the additional expertise and counsel of specialists in those operations.

It is assumed that the instrument will be administered as a personal "one on one" interview; and

1. The interviewer may require medical training and/or background in order to interpret many difficult clinical terms for the respondent.

2. The interview may be facilitated by being part of a complete medical evaluation.

3. Visual aids, such as photos of the special skin conditions, might be provided for review by the respondent.

4. The temporal relationship of disease occurrence to time spent in Vietnam may require more detailed probing.

5. The intent of this study questionnaire should be weighed in terms of this being a "one shot" interview vs. periodical reassessment over several years.

The questions included in the instrument are very thorough and comprehensive. Major areas of questioning which are oriented to the alleged complications of herbicide orange exposure include skin (chloracne), liver problems, gastrointestinal, neuropsychiatric, urinary tract, birth defects and cancer among others. Within individual sections it may be difficult to assess the quality of information returned. For example, no special definition of chloracne is given in the skin section. The type of response will be affected

by this lack of information. The reproductive history of the Vet does not clearly delineate all possible offspring. I think this may be more a problem of formatting than actual information gathering.

Focusing on the major concerns of the vet is important; and as well, it would enhance the data intake to make some effort to eliminate certain aspects of the medical inquiry, based upon severity of disease, consequences of acquiring certain diseases, and morbidity, both now and in the future of a particular individual. In this context, the contents of several sections have very specific diagnoses to be reviewed by the respondent. Several of these are rare, (eg. XANTHOLASMA - if spelling is correct it is not in Dorland's Medical Dictionary!); others are signs of pathology (eg. SPIDER ANGIOMATA) which may not be known in medical terms by a respondent. These should also be explained or eliminated. If such questions are administered by other than medically trained interviewers and, if they are answered in the positive, they may require further (?medicolegal necessity) follow up by medical resources.

Since the instrument is very comprehensive it will involve considerable respondent burden in terms of time. Several of the questions appear to need reformatting. Such alterations will <u>increase</u> administration time. Questions asking for specific data on Vietnam appear in several sections of the instrument. These may need collating into one section for uniformity of presentation and ease of response. Intervals spent in the service and in Vietnam would be helpful to assess exposure. Questions about rank, brigade, battalion and company, etc. might be included. Military service number and SSN might help to identify personnel and to validate data obtained.

It is difficult to draw conclusions about this instrument. It is a very comprehensive and a good first effort. The quality of information depends upon the type of interviewer used; improving formatting of several of the questions; the explicit orientation of the instrument - whether it will make every effort to put answers in a temporal perspective that is, before, during and after the Vietnam era.

It is a good beginning for the V.A. Study, but would require reworking. I would suggest taking advantage (if possible) of the rather extensive effort made by N.O.R.C.. They participated in the development of the U.S.A.F. Operation Ranchhand instruments. My recollection is that there are many similar types of questions.

Reviewer "I"

Feb. 24, 1982

RE: Comments on the UCLA protocol

TO: Vernon Houk, M.D.
Chairman, Science Panel of the Agent Orange Work Group

This version of the protocol reflects increased input on the part of the authors and studied responses to some of the comments provided on the first draft.

The sheer mass of the present state of the protocol has precluded a detailed review. There are, however, some questions which have been identified:

Questionaire

The questionaire seems terribly long. While the introductory portion discusses the questionaire, the quality control, the pilot study, etc. and gives the general assurance that the problem of interviewee fatique has been considered, I could find no speicfic mention of the length of time involved in filling out the questionaire.

Another area that would seem to anticipate interviewee fatique/frustration is the plethora of medical terms used in gathering information on medical histories. While this precision is probably needed for this type of sutdy, it must be recognized that the vast majority of the subjects will not be knowledgable about these conditions nor will the terms used be intelligible to them. Consequently, care and patience will have to used with the subjects as they respond.

The questionaire asks a large number of questions about the names and locations of doctors who have provided medical services in the subjects' past. I suspect that this information, too, will be difficult to recall and will lead to further frustation/fatigue.

Multiple Comparisions

On page 106 there is general recognition of the fact that multiple comparisons will be made on the same population during this study. This problem has been of concern from the beginning. It is still not clear what specific process(es) will be used to deduce the significance of the correlations found in

the study.

Inclusion of case-control study

A case-control study may have to be included within the cohort study. The statistical discussion shows that there is a low probability of finding an effect for total cancer, let alone a more specific type of cancer, which is more likely the case. With the careful attention to exposure in the protocol, a case-control study should be feasible.

3 March 1982

SUBJECT Evaluation of the Revised Initial Draft Protocol for Epidemiologic Studies of Agent Orange, Dr. Gary H. Spivey & Dr. Roger Detels Co-Principal Investigators

TO: Vernon Houk
Chair, Science Panel
Agent Orange Working Group

1. The following comments represent my personal opinion and not that necessarily of my organization.

a. Focus of the Study.

(1) The investigators have elected to focus the epidemiologic investigation on Agent Orange to the exclusion of other exposure factors. While this is an accepted and most often used scientific approach, i.e., single factor analysis, such studies can produce the need for other single factor studies until all likely possibilities of disease causation have been exhausted. If the concern of the Vietnam veteran persists and is demonstrated by a continuous parade of actually ill veterans, then one could begin the sequential search of two factor (exposure) studies, i.e, this would begin the examination of antagonistic, additive and synergistic effects. Ultimately, this process depending on the interest of the nation and the persistence of the veteran could extend for decades.

(2) Another but equally acceptable scientific approach is to include all or a reasonable number of factors in the first study to determine and document the existence of excess morbidity and mortality. The advantage of this approach is that if no excess of morbidity or mortality is found one could logically argue that for Vietnam veterans as a group the risk of disease and death as a result of serving in Vietnam is no different from that of other military personnel who didn't go to Vietnam. Additionally, such an approach allows the time compression of several single factor sequential or simultaneous studies into one simultaneous study.

(3) It is recommended that the Veterans Administration assess the feasibility of performing a multivariate type study before settling on the proposed single factor study. This could be done under the auspices of consultant contracts with statisticans familiar with methods of multivariate analysis. One such individual is Dr. Don Jensen, Virginia Polytechnic Institute and State University, Blacksburg, Virginia. He can be reached at (703) 961-5367.

(4) Lastly, the study cohort design proposed by Dr. Bricker is an intuitive apporach to such a multivariate study, why not go beyond that and actually try to design one?

b. Inclusion of Officers and Multiple Tour Personnel. While one can understand the desire to conduct as simple a study as possible, the recommendation that officer personnel and multiple tour personnel not be included goes against some toxicologic fundamentals. Namely, that physiologic response is often exposure level and time duration dependent. The fact of socio-economic status perhaps modifies the response but may not eliminate it. Therefore, recommend that officer and multiple tour personnel be included in the study.

c. Inclusion of Pre 1965 Personnel. While I understand that the herbs tapes do not extend back before 1965, this single fact should not be used as a basis for excluding pre 1965 personnel from the study. A goodly number of these people are likely the multiple tour individual who experienced the rigors of Vietnam to a greater extent than did perhaps his fellow veteran who arrive in post 1965. Their numbers are not so small as to be scientifically insufficient. In fact, the DoD Selected Manpower Statistics, fiscal year 1980 book shows on page 151 that for the years 1960 to 1965 the inclusive total manyears of effort were 239,300. Sixty-two percent of this effort was contributed by the Army.

d. Pilot Study. The concept of a pilot study is a good one. However, since the contractor proposes that multiple physical examination sites be utilized for the full study and includes any necessary laboratory analyses which are time sensitive, recommend that the pilot study include multiple sites with an evaluation of the laboratory measures included.

e. Quality Control. Since the protocol designers recommend multiple site examination points, an extensive quality control program needs to be developed. The Veterans Administration needs to begin assessing the between laboratory variability and to begin the development of a quality control program for testing at the time of the physical examination pilot test.

23 February 1982

SUBJECT: VA Herbicide Study

2. Included in this overall assessment are the outstanding components of questionnaire content and technique and the entire physical and psychologic health examination. Prime problem arees are summarized as follows:

a. The pilot study should be done if possible.

b. The proportionate mortality studies previously suggested by the contractor are not enveloped in the current Protocol but must be included.

c. The "multiple exposure concepts," based on short-term versus long-term degradation of Herbicide Orange components may create more problems than they will solve; notwithstanding, if they are to be used, the ecologic literature on environmental fate should be used more extensively to construct alternative or supplemental likelihood indices.

d. The proposed omission of re-enlistees, officers, and battle casualties is a mistake. If the proposed study design prevails (study of high-low exposure groups), these factors should be handled by appropriate matching.

e. To start the historical cohort at the time of exposure may well be incomplete for a total and proper fertility analysis.

f. While the possibility of a follow-up 25-35 years post-exposure is recommended for endpoints like cancer, the follow-up phase as a separate, discrete and bonafide study phase is not sufficiently emphasized.

g. The procedure for separating confounding effects from exposure should be clarified. It appears that the confounders (i.e., insecticide exposure, combat stress, endemic disease) will vary proportionately with increasing likelihood of exposure.

h. The proposal to establish populations at risk, from which to draw high and low groups based upon an "exposure likelihood index" may have very substantial difficulties requiring in-depth analysis. Specifically:

(1) The high-low design may be less powerful than using the full exposure gradient. Use of the full gradient will assist in uncoupling confounding factors and assist in interpreting distorted dose response curves.

(2) The likelihood index relies heavily on the HERBS tapes which are known to be substantially inaccurate.

(3) It is unknown (unlikely?) that all appropriate Company records reflect the use of herbicide spraying in the area, as well as helicopter or backpack dissemination.

i. There is minimal discussion of the use of alternate study groups, a prime hingepoint of the entire VA effort. The design concept of high versus low is not accompanied by any mathematical estimation of the exposure differences between the two groups. It would be tragic at the end of the study to determine that there was no substantive difference between the two groups, rendering the entire VA effort to a "numerator study." Specifically, adequate concern is not focused on the concept of a zero-exposed control group, nor the sole selection of helicopter pilots, backpack personnel, etc., as the prime study group.

j. Cited survival analysis methods emphasized incidence and prevalence statistics, omitting due concern to more refined life table and survival curve analyses. Also, issues of competing risks and "time to event" statistics may be of substantial value in assessing morbidity patterns, since temporal patterns of disease (age at onset) may be statistically different before such differences are evident in overall incidence or prevalence figures. The Protocol does not adequately address statistical power in general. Although the Protocol emphasizes a matched design, the logistics of appropriate matches may well be outweighed by a stratified design of a slightly larger sample size. Statistical power considerations, as well as overall cost, should be used to select the final design. The following are minor observation points on the generally outstanding questionnaire and physical examination.

(1) The birth defects section should use the same coding system as the CDC study to establish comparability. The questtionnaires should contain specific bias indicators as well as verifiers (and the manner of verification should be detailed).

(2) General physicians should not be selected for the examination, but should be rendered by experienced and highly qualified internists. Strong consideration should be given to "blind assessment" protocols for the physical examination.

(3) The physical examination should be restructured to emphasize continuously or polytomously distributed variables to enhance statistical power of the examination.

(4) Consideration should be given to serologically test all participants for melioidosis.

3. We recognize the gigantic undertaking of this Government health study. It is clear that every layman, veteran, politician, and scientist will have viewpoints to contribute. From our experience in the RANCH HAND study, we believe that the Veterans Administration should realistically know that at least two, and probably three, years of intensive effort will be required to get this study past a pilot or vanguard stage. Selection of population at risk and an appropriate control group(s), coupled with a meaningful exposure designation, will continue to be the most challenging aspects of the VA study.

SUBJECT: VA Herbicide Study

1. The protocol outlines development of an "exposure likelihood index" and indicates that a gradient in the exposure likelihood is expected. The plan is to select "high" and "low" exposure likelihood groups for study. I believe that this design decision needs further analysis. Specifically, when equal numbers of participants are studied, is the high-low group design more or less powerful than that using the full exposure gradient, recognizing that the exposure index is a random variable? Aside from this question of study power, I favor further consideration of use of the entire gradient for two reasons: (a) use of the entire gradient may help uncouple confounding factors (eg. RVN effects from herbicide effects), and (b) use of the entire gradient protects against an inverted "U" shaped dose-response curve.

2. The outline of the exposure likelihood index is interesting, however, I believe that it would be of significant value to seriously consider ecological modeling and calculational methods that are available in the literature to help evaluate environmental persistence of agent and its transport through air, soil, water, animal and vegetative compartments.

3. Survival analysis methods indicated in the protocol seem to emphasize incidence and prevalence statistics. I believe that life table and survival curve analyses should also be considered. Also, the investigators should be al to the possibility of competing risks. "time to event" statistics may also be value in assessing morbidity, since temporal patterns of disease (age at onset) be statistically different before such differences are evident in overall incidence or prevalence figures.

4. The protocol indicates a matched design, although the discussion of statistical methods does not reflect this design. Since potential population groups are large, the logistical cost of matching could outweigh advanteges. It may be far cheaper to work with slightly larger independent samples to preserve power than to perform the extensive record review needed for matching on several variables (McKinlay, Biometrics, 33, 725-735, dec., 1977).

OTA
March 1982

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REVIEW

of the

Protocol for

Epidemiologic Studies of Agent Orange

Office of Technology Assessment
Congress of the United States
Washington, D.C. 20510

March 1982

CONTENTS

REVIEW OF AGENT ORANGE EPIDEMIOLOGIC STUDY PROTOCOL

1. Introduction

The present, revised Protocol for Epidemiologic Studies of Agent Orange, submitted by Gary Spivey, Roger Detels and their colleagues at UCLA School of Public Health is vastly improved over the first document presented for review in the fall of 1981. The revision contains adequate detail to permit thorough review and criticism. Necessary documentation for the recommended study design is described in a series of appendices. It is clear that the investigators have had opportunities for discussions with the Department of Defense and Veterans Administration personnel, reflected in the more realistic approach to details of data acquisition.

This protocol for a study of the possible long-term health effects resulting from exposure of United States troops to Agent Orange is worthy of approval as the basic framework for a detailed study design. After acceptance of this protocol by VA, the next required step will be completion of a detailed, logistically complete plan for the pilot study. The current protocol complies with the desires of Congress and the VA and describes an epidemiologic study that can probably be executed. The detailed planning for and execution of the proposed pilot study is necessary to answer adequately questions that remain about the feasibility of a full scale study.

Optimism about the protocol and the study was not universal among the OTA Advisory Panel members. Some panel members, while commending the UCLA team for their industry in writing a protocol of this complexity and their ambition in the scope of their proposal, expressed great reservations for the project. These feelings represent a lingering disagreement about whether such a study should be done at all, and to a lesser extent whether the current protocol is adequate to the task. The pessimism stems principally from two sources: the undeniable fact that

the investigators are proposing to embark on a very general search for disorders of various organ systems, and the circumstance that exposure to the agent was at variable dosage levels and took place between 10 and 15 years ago. In view of such reservations it is important that the investigators clearly describe the limits of the study, and that the decision to continue be based on estimation of the kinds of health effects detectable by the study.

The current protocol focuses exclusively on the historical cohort study. The preliminary morbidity and mortality studies, proposed in the August 1981 document, have been dropped. This change has strengthened the protocol considerably, and we understand that the VA will, in all probability, be conducting a mortality study of some type, filling the gap left by removal of such a proposal from the UCLA protocol.

OTA recognizes and applauds the tremendous effort that has gone into preparing the current document. Given the short time which the investigators have had for revisions, the product is of very high quality. No such document can, however, anticipate all problems which will arise in the conduct of a complex investigation. If the study goes forward to the pilot phase, the selected contractor should begin preparation of a detailed manual of operations fully describing all features and procedures of the study.

2. Timetable

An overall study length of five and a half years, divided into two and a quarter years for development and pilot testing, two and a quarter years for implementation of the full protocol and one year for data analysis is proposed. The division into stages is appropriate and the initial stage is about right in length. However, the implementation and analytical stages appear overly optimistic,

allowing little or no time for enrollment, scheduling and the general milling around which is the inevitable concomitant of any large, complex, multi-institutional study. An overall length of at least 7-1/2 to 8 years seems a more reasonable planning horizon for this investigation. Time estimates can be refined as planning progresses.

3. Checkpoints

The investigators have identified a number of points at which progress should be evaluated and the study halted if certain criteria are not met. OTA endorses such step-wise decisionmaking and cautions only that the criteria for making decisions concerning continuation must be stated clearly in advance.

Obvious checkpoints involve several issues discussed in this review. For example, early in the detailed study design the following questions must be addressed:

1. Can troops be successfully assigned to high or low likelihood of exposure categories?

2. Are there sufficient numbers of troops in each cohort to carry out a meaningful study?

3. Are the endpoints to be examined sufficient to justify executing the study?

A negative answer to any of these questions should result in calling a halt to the study and a rethinking of possible approaches to learning about possible health effects from Agent Orange.

Oversight group

Oversight Committee

The proposal that an oversight committee of eminent scientists be empaneled to guide the pilot and full operational phases of the study is excellent and should be adopted without question. Representation from one or more of the veterans' organizations also should be considered. Such a committee will provide a buffer for an investigation of great public and personal sensitivity. The committee should be appointed as soon as possible, to be available during planning for the pilot study and to play a key role in the "checkpoint decisions" of whether to proceed through the stages outlined in the protocol.

5. Pilot Test

The investigators propose an overall pilot test of 2-1/4 years involving 400 participants and a single examining center. The time allotted for and size of this investigative phase seem appropriate. However, the choice of a single examining center, though defended, may be unwise. Lack of standardization and comparability between centers will be one of the most difficult problems in the full study. To conduct a pilot study which provides no information in this area would be regrettable. At lease two pilot centers should be identified.

6. Limits of the Study

Before pilot testing can begin, the limits of the study must be clearly drawn. Statistical probability dictates that, for a study of any size, no matter how perfectly designed, effects occurring with low frequencies, as a result of an exposure, may, by chance, not be observed at all. The ability to detect effects at lower and lower frequency increases with the number of participants, but there are always limits.

A different limitation of this type of study is that of determining causation. Even if a study is sufficiently large to be clearly significant statistically, it is at times impossible to conclude that an excess of effects seen in exposed subjects is caused by the exposure studied. The alternative explanation must be considered that the exposed subjects were a more vulnerable group initially and would have experienced the effect more commonly whether or not they had been exposed. This problem cannot be solved by including large numbers of subjects, even if very large numbers are available for study. The problem can be alleviated if it is possible to study the subjects carefully and to determine that they were not initially different in any important way. If there is a strong association between exposure and effect, and if the two groups seem to have been generally similar before exposure, it is reasonable to conclude that a large effect is probably due to the exposure. But if the association is weak, so that the effect is only a little more common after exposure, it is generally impossible to be assured that some minor initial difference between exposed and not exposed is not the true cause. The requirements here are both adequate number of subjects and adequate strength of association.

These two limitations, that imposed by a limited number of participants and that of limited ability to infer causation, are both pertinent to the proposed study. The total population of Vietnam veterans is finite, and very rare events such as certain malignant tumors at these young ages may be undetectable because of sample size, even if they are strongly associated with Agent Orange exposure. On the other hand, some common effects may indeed be due to Agent Orange, with only a slightly increased frequency. In these cases, large numbers of exposed subjects may experience the effect, but it will also be seen in large numbers of non-exposed men. Even if a difference is demonstrated and with the large numbers of cases is highly significant, it cannot be assured that the excess is not due to some initial vulnerability of the exposed. or to confounding factors of other sorts.

Probably the main strength of the study is that it will provide upper estimates of the magnitude of each endpoint for which analysis is carried out. Upper estimates will be available even for rare diseases and diseases weakly associated with exposure. But only for diseases sufficiently common to occur in large numbers and which are also strongly associated with Agent Orange will clear demonstration be possible that the disease is due to this exposure. There may be no such conditions identified.

7. Structure of the Study

The investigators have suggested a number of procedural mechanisms to be considered as the details of the study are developed. These basically concern responsibility for conducting interviews and medical examinations and the sites of such activities. Though these logistical aspects need not necessarily be decided in the scope of the current contract, the Panel made some suggestions. The investigators raised the possibility of using VA medical facilities to carry out the examinations. The Panel did not reject the idea of using VA facilities, but a number of concerns were expressed. Some of these issues were raised in OTA's review of the first draft protocol, and are mentioned in the current protocol. There is long-standing concern about various factors which might affect participation rates, and it may be that some veterans would be deterred from participating if the examinations were to be carried out at VA hospitals. Before any decision is taken to use VA hospitals for the full-scale study, the effect on participation should be determined during the pilot study.

An encouraging note in this regard is that, currently, about 3,000 veterans monthly are examined as part of VA's Agent Orange Registry. This participation may be interpreted as showing that veterans will participate in a study in VA facilities.

An organizational structure for conducting studies already exists within the VA, namely the Cooperative Studies Program (CSP) which conducts collaborative clinical trials among VA hospitals. The organizational structure for each clinical trial within the CSP consists of a chairman's office and a designated biostatistics research support center (of which there are four around the country) who together coordinate the study and perform monitoring, quality control, and analysis. There is an external Operations Committee that meets periodically and reviews progress and adherence to the protocol. This background of experience in conducting collaborative research within the VA, with an organizational structure similar to that proposed by UCLA, could be valuable to the investigators in fleshing out the details of the protocol.

Aside from the possible effects on participation rates of using the VA medical facilities, the other major concern, and perhaps the more serious one, is the problem of standardization among personnel and procedures in the examination centers. This will be a thorny problem regardless of who conducts the examinations. The opinion was expressed and supported that it might be more difficult to achieve standardization in the VA system than in other health facilities.

A suggestion that garnered nearly unanimous support of the Panel was to consider contracting with the National Center for Health Statistics (NCHS) Health and Nutrition Examination Survey (HANES) for both the interview and the medical examinations. This program uses mobile examination facilities. The purpose of HANES is health assessment (as opposed to the treatment orientation of most general medical institutions) which is exactly what is needed in this type of study. The usual complement of HANES study personnel might have to be augmented by neurologists and other specialists for this effort, but that should pose no major problem. HANES personnel are accustomed to following strict protocols, and are equipped to gather

and analyze biological samples. Collecting and storing biological samples might be considered as part of the study. If pertinent new tests become available, they can be run on the stored samples.

OTA urges the investigators and VA to consider HANES or another equally qualified such group. (For a brief description of HANES see Attachment A.) Regardless of the organization performing examinations, the appropriate referral would be made for any condition requiring medical attention, whether it be to a VA facility or to the participant's private physician.

8. Cooperation and Coordination Among the Organizations to be Involved in the Study

Beginning with the pilot stage, the Agent Orange study will involve cooperative efforts on the parts of several organizations. Aside from the review groups such as OTA, the VA Herbicide Panel, the Agent Orange Working Group and perhaps the National Academy of Sciences, attention has to be directed at the organizations that will plan and execute the study.

First of all, the VA will have to decide upon a primary contractor to develop the detailed plan, and the contractor will presumably arrange subcontracts with other organizations to administer the questionnaire and medical examinations. If the suggestion in the protocol is followed, some agreements should be made with veterans organizations so that their good offices can be used to publicize the study and encourage participation in it. Furthermore, the relation between the Department of the Army, which will contribute to the exposure index, and the VA and the primary contractor will have to be detailed. The sooner the links can be made among all these organizations the better.

9. Exposure Likelihood Index

The contractors provide an orderly description of the steps necessary to prepare an exposure likelihood index. At the same time, the authors remain properly cautious about whether any index which can be constructed will have a useful degree of correlation with likelihood of exposure.

During the time the investigators were working on the present protocol, Dr. Jerome Bricker of the Department of Defense developed a different method for constructing an index (Dr. Bricker's scheme is included in the protocol as Appendix H). Dr. Bricker enjoys and benefits from a working relation with Mr. Richard Christian who, by general agreement, knows more than anyone else about the records necessary for the study of Agent Orange exposure in Vietnam. Dr. Bricker and Mr. Christian strongly hold the opinion that Dr. Bricker's suggested methods would be quicker and easier to use. Mr. Christian, who was at the OTA Advisory Panel meeting, said that his organization could provide an index based either on the UCLA or Dr. Bricker's proposal.

The UCLA protocol recommends that a member of the organization that will coordinate the study work closely with the Army in developing criteria for the exposure index. For example, the cut points that will establish whether a unit is considered to be in the high or low likelihood of exposure groups must be defined in a cooperative manner between the contractors and the Army. The protocol also recommends that the Agent Orange Working Group be involved in establishing the criteria that will establish which units are considered to be in different exposure groups. These are commendable ideas.

OTA did not decide which method of constructing an exposure index was better. Further discussion and collaboration between the contractors for the pilot study and

the Army and possibly the Agent Orange Working Group should lead to a decision about the preferred method. That is considered a detail best left to the designers of the study and the records experts.

a. Cohort Selection

The question of how an individual would finally be selected to a cohort based on likelihood of exposure received a great deal of attention from the Panel. There was concern that the problems of determining whether or not an individual was indeed with his company on a given day might be overwhelming. How much error would be introduced by the assumption that the entire roster of a company was present on a given day, leading to assignment of all company members to the same exposure status for that day? A test run on a few companies to determine how great a difference there would be between the group method and the individual method of exposure determination might be of value and should be considered. If the group method did not create a significant amount of misclassification (a level determined by the investigators before the test begins) the need to resort to the individual method might be obviated.

b. Third Cohort

About one year ago, there was a general impression that a study of Agent Orange was impossible. At that time, discussion began about a study of the "Vietnam experience" as an alternative to the seemingly-impossible Agent Orange study. Such a study would necessarily involve study of some comparison population not exposed to the "Vietnam experience," a third cohort. Since then, the efforts of the Department of the Army and the Agent Orange Working Group, with prodding from veterans organizations, have produced records that provide some assurance that exposures to Agent Orange can be estimated. That assurance, in turn, means that an Agent Orange

study can be mounted. The fact that an Agent Orange study can be mounted, however, does not mean that it will necessarily produce meaningful results or clarify important issues.

The contract placed with UCLA called for the development of a protocol for an Agent Orange study. OTA, in reviewing the protocol, has restricted itself to consideration of an Agent Orange study in contrast to a Vietnam experience study.

However, the issue of a "third cohort," a group of veterans who did not serve in Vietnam, was discussed at the OTA Advisory Panel meeting. Those who favored expansion of the study saw an opportunity to answer a number of questions by including the third study group. Those opposed to expansion cited the major problem of choice of endpoints to be included in such a study. Concentrating largely on health effects expected from toxic chemicals is seen as a necessary step in refining the questionnaire and medical examinations to study Agent Orange. If the study is expanded, other endpoints more directly related to war experiences will have to be considered.

c. Officers and Multiple Tours

The exclusion of officers and individuals with multiple tours of duty, as is proposed in the protocol, would be unfortunate in that these individuals may include a large proportion of the most highly exposed soldiers. The suggestion was made that such individuals be segregated from the others, but that no decision be made about excluding them until every effort was made to include them in the study. The difficulty in including officers and multiple-tour veterans in the study arises from the fact that the probability of a multiple-tour veteran's being in the low likelihood of exposure group is very small. A comparison of multiple tour exposed subjects with single tour unexposed subjects was considered uninterpretable because

of confounding factors. If that is the only comparison possible, the UCLA proposal to exclude officers and multiple-tour individuals should be supported.

10. Locating and Recruiting Veterans for Participation in the Study

The protocol thoroughly outlines steps for locating veterans. Certainly the use of IRS files to locate veterans would make the process more efficient. Permission for such use of IRS data is granted for National Institute of Occupational Safety and Health studies, and it should be sought for this study.

In contrast to the details provided about tracing veterans, there were too few about problems of recruiting the located veterans into the study. Problems with differential response rates, that is, differences in the willingness to participate among the low and high likelihood of exposure groups are mentioned, but no specifics are provided about what is to be done to improve participation. There is also a lack of discussion of the treatment of cohort members who already have died. Some data collection procedures must be developed for those individuals.

Compensation for time lost from work, and perhaps, additional money might be offered for participation. The Air Force is paying its Ranch Hand participants $100 per day. In addition, the appropriate referral should be provided for any condition requiring medical attention which is detected in the study.

Safeguards are necessary so that the initial letter and telephone contacts are handled in a similar manner for all participants. Offering different inducements for participation or making suggestions about exposure status could affect response rates. The recruitment letter needs careful attention. The wording of the sample letter provided with the protocol must be reconsidered. The present form and tone might generate avoidable non-participation.

The suggestion was made that the initial telephone contact might be expanded in order to gather some information. That conversation will be the only source of data for veterans who do not choose to participate. A standard inquiry about demographic and other characteristics should be made at that time if at all possible. The Air Force has developed a minimum data set for this purpose.

11. Outcome Assessment

The questionnaire and, to a lesser extent, the medical examinations are mosaics of question segments, mostly drawn from existing instruments, blanketing many areas of possible health effects. The investigators propose to provide as much overlap in data collection as possible with other concurrent studies, particularly investigations of Australian veterans of Vietnam and U.S. Air Force Ranch Hands. This is a strength of the study and should be encouraged. Replication of any findings, whether positive or negative, will strengthen all the investigations.

While OTA appreciates the value of including questions from other studies, there is some unease about the lack of justification for the questions and the seeming lack of focus. There is a need for the investigators to relate questions to the purpose of the study. This exercise is the first step toward developing an overall scheme for interpreting the results. It is a difficult exercise even when dealing with objective information, and it is all the more difficult when dealing with so many largely subjective responses. The interpretive value of various answers and combinations of answers may be, next to the assignment of individuals to the low and high likelihood of exposure groups, the most controversial aspect of the study details. It is, therefore, important that the development of the analytical scheme be carried on in tandem with development of the likelihood of exposure index.

A fundamental point, discussed in our September 8 review of the first draft protocol, is reiterated in the current review: the investigators must specify at least some key outcomes they intend to look for. OTA does recognize, however, that there is merit in looking for as wide a range of outcomes as possible in view of the plethora of complaints alleged to be consequent to Agent Orange exposure. Allowance should be made for some looseness in data collection, for the examination of broad, open-ended hypothesis-seeking questions. The investigators could easily be faulted for failing to look for particular complaints after the study is completed. This does not alter the fact that decisions will have to be made to investigate thoroughly a small number of key conditions most likely to be associated with Agent Orange, and to exclude those for which little or no support exists. Decisions about key outcomes should be based on previous epidemiologic and animal studies of the components of Agent Orange and perhaps other toxic chemicals, if deemed relevant. The decisions should also take into account some of the more frequently-occurring effects reported in the popular press.

There is bound to be disagreement about the key endpoints chosen initially, but the sooner the initial list is drawn up, the greater the chance for constructive input from reviewers, and the happier everyone is likely to be with the final product. The question of key endpoints must be settled before the questionnaire and medical examinations can be made final.

a. Questionnaire

The veteran and spouse questionnaires are made up of questions about health, and non-health characteristics, broadly described as demographic, lifestyle and occupational descriptors. The questionnaires are made up, in large part, of questions and sections drawn from other questionnaires, including the Australian Agent Orange study, the Air Force's Ranch Hand questionnaire and several other

general health and lifestyle questionnaires. The questionnaires were generally considered to be the weakest part of the protocol. There was strong feeling that a major overhaul is necessary both in substance and in form before the questionnaires can be used. There was some concern that the interview required to complete the questionnaire would take too long. This was tempered by recognition of the need to acquire hypothesis-seeking information which, of necessity, may be poorly delineated. At this time, overcollection is preferable to undercollection. The Panel strongly suggested arranging the sections or questions in the questionnaire and other data collection instruments hierarchically, from the inquiries most vital to those least likely to produce useful information. This hierarchy could guide eventual paring down of the questionnaire if deemed necessary after further field testing. A general suggestion was to encourage the study designers to enlist the help of experts in designing the questionnaires.

The Panel was unclear about the setting in which the questionnaire is to be administered. Some members expressed a preference for administering it, all or part, at some time prior to the medical examinations, and not necessarily at the examination site. If more convenient and numerous locations for the interview could be arranged, e.g. public schools or other public buildings, participation levels might be enchanced. Interviewing in the participant's home was not favored, since this might discourage participation among a subgroup of veterans, including perhaps those who have not shared their Vietnam experiences with their families. This same concern, if it pertains to a large number of veterans, may pose a problem in attaining sufficient participation of wives.

Depending upon the length and content of the questionnaire that eventually is adopted, some thought might be given to "staging" its administration. This ties in with another issue concerning the training and background of interviewers. There

might be merit in considering the use of trained medical personnel -- nurses or physicians' assistants, for example -- to administer the health segment, and other trained interviewers to cover the non-health questions. It might be possible, for instance, to administer the questions on demographics, lifestyle and occupation prior to the time of the medical examinations. This might be particularly advantageous if the questionnaire is long.

Concern was raised that, particularly in the health segment and in the questions dealing with exposures to chemicals both in and out of Vietnam, there was little or no allowance for spontaneity on the part of the participants. Valuable information might be volunteered if the opportunity exists for participants to fill in gaps left by specific questions.

The general health segment suffers from being too broad and sweeping, and the segments concerned with specific key areas do not go into enough depth. This is in large part a consequence of the lack of focus on specific key health outcomes related to Agent Orange. As presented in the questionnaire, the systems of the body were very unevenly covered. The language used for different systems varies from vague and possibly misleading vernacular to highly specific esoteric diagnoses. A potentially fruitful area of inquiry, infectious diseases, received no attention at all. Information about parasitic diseases, specifically, should be sought.

OTA feels strongly that both diagnoses and symptoms should be sought for all conditions of interest and that certain responses should trigger in-depth probes in key areas. The Panel suggested various models that the investigators might draw from for presenting diagnoses and symptoms, specifically the Kaiser Foundation medical history questionnaire, the Cornell Medical Index and the health history questionnaires of major insurance companies.

The questions relating to neurology are in need of revision. More emphasis should be placed on functional questions in this area. For example, probing about specific skills that the participant possessed in the past compared with his abilities now could uncover changes in neurologic status. The questions should be restated and terms added to be more inclusive in describing sensations. These were not well-described.

The approach to malformations in offspring was considered deficient. The spouse questionnaire is not specific enough about exposures of the mother during each pregnancy, and no attempt is indicated to interview or obtain records of previous partners or spouses. Questions about smoking and drinking should be asked specific to each pregnancy. Questions about medications known to be teratogenic should be asked directly. No information about pregnancies resulting in perinatal deaths, often occurring in babies with birth defects, is gathered. This should be corrected. If a birth defect is reported by either the participant or spouse, an attempt should be made to verify the diagnosis via medical records.

b. Laboratory Tests

The laboratory tests included in the protocol were heavily criticized as inappropriate and generally not leading to any conclusions about exposure to toxic substances. OTA recognizes the difficulty in choosing appropriate laboratory tests, however, since none is specifically diagnostic for the effects of Agent Orange or its constituents. The point was stressed that the participants will be relatively young and healthy, and for the most part we should be looking for early markers of disease and not frank undiagnosed cases of most conditions. The selection of the study participants on whom the tests in Table 3 will be performed is not discussed. Just as for questionnaire and other medical examination items, the

justification for laboratory tests should be included, and the conditions that can be detected by them, either alone or in conjunction with information from the questionnaire and physical examination, should be specified. In light of the recent publicity about melioidosis, some serological testing for evidence of exposure to infectious diseases might be considered. This is not advocated, however, if the tests available are not well standardized or accepted as meaningful.

An example of the potential difficulty in interpreting laboratory tests was brought up by one panel member. Laboratory values obtained from an individual might have no relevance whatsoever to an individual's exposure status in 1969. This is important because aberrations in levels of many enzymes, hormones, etc., are often reflective of acute rather than chronic conditions. For example, an elevated urine white blood cell count could be the result of a lower urinary tract infection occurring one week before the sample was drawn and not have any relevance to an individual's Vietnam experience. Therefore, one aspect of the rationale for interpretation is to put into proper perspective the meaning of aberrant levels detected in laboratory tests.

Another aspect of interpreting these types of laboratory tests involves the reported result itself. Most laboratory tests have published reference ranges or so-called normal ranges, which are considered to be important clinical tools. There is, however, some controversy regarding their utility for epidemiologic study. What does it mean if the study group has more individuals with values outside a given reference range than the control group? Does it have biological significance or is it a consequence of the reference range's being too narrow for this group? In some cases, actual values can be reported (e.g., hematocrit, percent lymphocytes) and analyzed, circumventing the problem of the reference range. However, with variables such as urine protein, the values are usually reported as being within or outside

the reference range and interpretation is difficult. Perhaps such variables should be considered only with respect to an individual's clinical presentation and not considered as epidemiologic outcomes.

Another related problem involves the possible finding of a significant difference between study and control groups which cannot be biologically explained. For example, what does it mean if the study group has significantly elevated red blood cell counts, a condition usually not considered detrimental? Will this be reported as a cause for concern?

There are, then, at least four areas pertaining to the analysis and interpretation of the laboratory aspects of the study which require guidelines for interpretation: the meaning of aberrant levels detected in laboratory tests, the significance and/or usefulness of reference ranges, clinical versus biologic interpretation of data, and a definition of areas of concern.

c. Physical Examination

The physical examination included in the protocol is adapted from that to be used in the Australian study, and it is a good starting point for the VA study. Panel members made a number of specific suggestions, included in this review in Attachment B. Some general points also were brought out. The physical exam should be "Americanized," though comparability with the Australian study should be preserved as much as possible. Systems for scoring items and examination techniques should be based on current American practice. Training for the medical personnel carrying out examinations should not be devoted to learning new scoring systems. Some of the items in the examination are too general, where specific conditions should be noted.

d. Neurologic Examination, Psychologic Assessment and Neuropsychologic Assessment

The group of test instruments proposed to assess neurologic, psychologic and neuropsychologic status was generally considered strong. A number of improvements were suggested, the more specific of which are included in Attachment B.

The neurologic examination requires modification to focus more clearly on peripheral neuropathies. At present, some of the critical muscles are missed and appropriate examinations should be added. It was suggested that an audiogram be added as well. There are some questions requiring greater quantification and others requiring changes in explanations of the grading system. The question on mental status should be replaced with some objective measure, as the subjective remarks of the examiner would be difficult to interpret.

Regarding the psychologic assessment, the MMPI and SCL-90 have their strength in measuring depression and anxiety. An effect, if present, should be evident with these tests. SADS-RDC is not considered the "state-of-the-art" in many diagnostic categories, though for schizophrenia it is probably the best. NIMH is performing a cross-sectional screen on 15,000 individuals using a new scale called DIS. Supposedly it can differentiate schizophrenia, depression, phobias, obsessions, drug abuse, alcoholism and anti-social behavior with the last three items being the strongest. This obviously would be important in the veteran population. Since the scale for schizophrenia was weaker in DIS, the possibility of creating a hybrid between SADS and DIS might be considered. The DIS can be administered by a lay person and takes approximately 90 minutes.

The neuropsychologic test battery is well chosen for measuring effects of any brain damage if present. The sensitivity will be increased if results can be compared to test results from the veteran's induction examination. One Panel member

sounded a cautionary note about factors that must be consiered in interpreting test results. In addition to age and education, native language is important. Verbal fluency in the controlled word associations and vocabulary are two examples that might be significantly altered by a native language other than English. The questionnaire at present does not include an inquiry about native language. Finally, it appears that these tests will take longer to administer than has been estimated in this protocol.

e. Release of Medical Records to the Study

The protocol proposes that the study contractors request release of participants' medical records for use in the study. In general, there was a feeling that such records would have limited value. Concern was expressed that Agent Orange is such an emotional subject that a participant who presented himself to his family physician claiming ill effects from exposure might receive examinations and diagnoses different from a person who did not think he had been exposed to the herbicide. Additionally, it would be difficult to determine possible biases introduced by use of some medical records but not others. It was suggested that the time to make a final decision on this would be at the completion of the pilot test, when the yield from such an effort could be assessed.

Army induction examination records might be useful in establishing baseline values for some measurements. Those records suffer from many shortcomings, but they are collected in a routine manner, and they might be of value in the general health and psychologic areas. The usefulness of those records should be assessed.

If the effort is made to obtain medical records from participants, provision should be made for requesting release of children's medical records, as well. Such records would be of value in determining whether a birth defect might have resulted from exposure to toxic substances or from another cause. Likewise, medical records

from ex-partners might be useful in the case of children borne by women other than the current spouse or partner.

12. Data Analysis and Sample Size

The discussions of data analysis and sample size were well presented and thorough treatments, at least for certain aspects. However, there is no discussion of how confounding variables are to be handled in the analysis. This subject must be further developed.

The data analysis plan seem clearcut and logical. The notion of obtaining a handle on reporting bias is laudable. However, it is not clear just how a comparison of "those reporting exposure but not verified to have had exposure with those verified to have had exposure but not reporting exposure" (page 101) will provide the requisite information. Further, if this comparison shows some meaningful differences, what then will the investigators do in analyzing their results?

The remaining statistical analyses are generally straightforward, and and well presented, if not in full detail. Since there presently exists a fair degree of vagueness regarding the particular health outcomes implicated, the investigators cannot be faulted for their lack of detail regarding statistical analyses.

The sample size determination, made with reference to the limited information now available, is clear and pertinent to the proposed study. The requisite sample size, as the investigators indicate, can be more firmly determined following completion of the pilot study.

The choice of 0.01 and 0.05 for type I and type II error probabilities, respectively, is unusually severe. The investigators should consider relaxing the type I error at least, perhaps to the more customary 0.05 level. Adhering to a level of 0.01 seems to move this research study unnecessarily into a decisionmaking arena. Strength of association should be expressed by point estimates along with pertinent confidence intervals.

The choice of a 30% cutoff for combined nontraceability and refusal to participate raised concerns that such strictness might make the study impossible. An overall participation rate of 70%, which the investigators require, would be considered quite good for many studies but, according to the Panel, would likely be unachievable in this case. A somewhat lower participation rate was thought to be more realistic. Obtaining minimal information on essentially every participant at the time of the initial contact would reduce the impact of non-participation. On the other hand, adhering to the criterion of a difference in participation rates of no more than 15% between the high and low likelihood of exposure groups is considered appropriate.

13. Summary

The protocol submitted by the contractors at UCLA in January 1982 is worthy of approval as the basic framework for a study of the long-term health effects resulting from exposure of United States troops in Vietnam to Agent Orange. The choice of study design, a comparison of two cohorts defined by estimated high and low likelihood of exposure, is appropriate.

Detailed planning leading to the pilot study should continue and go/no go decisions made at the "checkpoints" specified in the protocol. The oversight

committee, proposed by the investigators, should be appointed without delay to be available during planning for the pilot study.

In the planning process, two objectives should be clearly addressed:

1. Hypothesis testing of a small group of key health outcomes, suggested by toxicologic considerations and by presently accumulated reports of presumed exposed subjects; and

2. Hypothesis generation about health outcomes not anticipated.

The questionnaire requires major revision, while the physical and neurologic examinations, and the psychologic and neuropsychologic assessments require fewer changes. Suggested laboratory tests also require reconsideration.

The OTA Advisory Panel made a number of suggestions for improving the study plan, which are included in this review.

Finally, the limits of the study must be laid out clearly for those groups and individuals who will ulimately make decisions about whether to proceed along the course as it has been laid out.

Human rights committee & veteran representation

Hierarchic questions, exams, etc. & progressive steps defined, i.e. algorithms

Separation of military-exposure & other history

ATTACHMENT A

Health and Nutrition Examination Survey (HANES).—HANES, initiated in 1970, is a modification and expansion of the earlier Health Examination Survey (HES). These surveys collect and use data from interviews and physical examinations to estimate the prevalence of chronic diseases, establish physiological standards for various tests, determine the nutritional status of the population, and assess exposure levels to certain environmental substances. The sampling techniques employed provide representative national data. Two surveys, HANES I (1971-75) and HANES II (1976-79) have been conducted. Both surveys examined approximately 20,000 persons.

HANES is the most extensive national assessment of health and nutritional status of the American people. The nutritional component of HANES includes: information on dietary intake; data from hematologic and biochemical tests; body measurements; and chemical examination for various signs of high risks of nutritional deficiency. Preliminary findings from the HANES II pesticide monitoring program have found an apparent rise in tissue levels of DDT and PCBs. The implications of the observed levels are uncertain.

HANES surveys might become valuable sources of information for cancer epidemiology if sufficient resources were available. Because of its representative nature, aggregate data from the survey can be used to represent "normal" or background levels. For example, white cell count levels determined in HANES I were used for comparative purposes in an epidemiologic study of laboratory workers exposed to suspected toxic chemicals. HANES II contains certain information about dietary intake of substances which have been associated with a lower risk of cancer, vitamins A and C, and substances such as fats which are associated with higher risks.

HANES might be linked with other health data systems, such as the National Death Index (see below) to facilitate assessment of whether particular exposure levels or certain nutritional statuses were associated with cancer mortality. NCHS, with its HANES capabilities, has been asked to participate in studies near Love Canal, and to evaluate the health status of certain high-risk industry groups. It was unable to do so because of limited resources.

The NCHS overall monitoring survey budget for fiscal year 1981 is $28 million. This is a $3 million increase over 1980 and includes $1.1 million for a special HANES study which will focus on Hispanics in selected areas of the United States. The study is designed to describe the health and nutritional status of the Mexican-American, Puerto Rican-American and Cuban-American populations. Studies of specific groups are necessary to acquire data in sufficient detail to describe subgroups of the population which differ from the "average." General national surveys such as HANES I and II produce data about the "average" citizen by sampling groups in proportion to their representation in the total population, and this often results in too small a sample size to be useful for identifiable smaller groups.

From: Assessment of Technologies for Determining Cancer Risks from the Environment
Office of Technology Assessment, 1981

ATTACHMENT B

Specific Comments of Panel Members

These comments on certain details of the protocol were made by members of the OTA Advisory Panel. They are included for the benefit of the contractors in further refining the protocol. When decisions about key outcomes, and about the breadth of the study are made, some comments may no longer apply.

I. Comments on Protocol Text

page 11 "Time-bomb" idea - imponderable but not necessarily improbable.

page 15 para 2, l.4 "known very heavy exposure to Agent Orange." Even in Ranch Hand, exposure is presumed rather than known.

page 20 para 1, l.2 "presumed highly . . . exposed." Even the higher exposure group will not necessarily be "highly" exposed. "Higher exposure group" might be more accurate.

page 25 Step 5, l.5 insert "likely," to read "number of likely exposures he encountered."

II. Comments on Questionnaires

page 10 Question concerning agricultural exposures needs more attention. An agricultural specialist might be consulted to develop a set of questions which would fully probe possible exposures to agricultural chemicals. Lists of all generic and trade names of chemicals should be supplied. Hygiene habits after exposure to such chemicals should be probed as well.

page 89, (e & f) Why are epilepsy, and convulsions or seizures separated when they are identical? How will it be rated if an individual answers yes to both versus just one?

page 89, (h) Head injury is often a problem of the past. It helps to determine severity by asking if loss of consciousness occurred, since such episodes are often treated in emergency rooms.

page 95 Double vision and blindness in one eye are too limited; should include dimming of vision in both eyes? or one eye?

A question should be included regarding cramping in the calves since this is a common presentation in early peripheral neuropathy.

Previous medication history is not covered. It is not enough to know what medications a person is currently taking.

Sexual preference is not queried. It is important to ask about this since homosexuals disease patterns appear to be different from that of heterosexuals.

A question about cocaine use should be added.

More questions dealing with "social health" should be included, covering marital history, migration, involvement with the criminal justice system, credit problems. These items could be verified through legal records.

The reproductive section of the spouse questionnaire inquires about labor and delivery problems only for live births. This should be expanded to include all births.

The spouse questionnaire should include questions specifically about use of anti-coagulants and spermicides, both of which may be teratogenic.

III. Comments on Physical Examination

Urinalysis does not use American dip-stick categories of 1+ to 4+. Also, room to identify the type of cast is needed.

A.7.d. "Nasal Mucosa Normal" is too general. There are specific abnormalities to be noted.

B.2. a&b. Not sure that one can safely differentiate acute from chronic otitis externa on a single examination. Need more objective findings.

B.2. c. Need a basic fundoscopic examination.

D.1. Need an objective determination of lymphadenopathy.

D.2. Room is needed for description of abnormalities.

E.4. Gynaecomastia - unilateral or bilateral?

E.5. Clubbing needs to be added, here or elsewhere.

E.6. Need respiratory rate.

E.9. This is an English-based classification, probably useful for this purpose. If used, we need anterior as well as posterior.

F.4. Need to describe how high jugular venous pressure is, not yes/no.

F.8. Need to distinguish ejection click from late systolic click. Also, splitting of S_1 and S_2 needs to be noted.

F.9. Americans rate murmur on a scale of 1-6. Also needed is an opportunity to assess the murmur.

F.10 a.b. These questions are very subjective. Should be asked only after questions of foot temperature, presence of ulcers or other skin changes. Pulses should precede any assessment of whether ischemia is present.

G. Probably need a question on whether guarding or tenderness of the abdomen. Also whether a pulsatile, enlarged aorta.

G.4. Need objective definition of hepatomegaly.

G.5. Need objective definition of splenomegaly.

J.a. Need to ask about prostatic nodules, rectal masses, hemorrhoids or other lesions.

K. Need room to describe positive findings.

K.8.a. Pain where?

L.3. Should include specific test for carpal tunnel syndrome.

M. Need room to describe positive findings.

M. 13. Need objective definition of obesity.

M.14. What is the purpose of this question?

Possible additions to physical examination.

-presence of xanthoma, xanthelasma
-presence of pallor.
-body habitus (e.g. Marfanoid)
-other endocrine-related conditions -- feminization, body hair, striae, dorsal hump - fat distribution, Achilles reflex relaxation phase.

IV. Comments on Laboratory tests.

Semen analysis must be specifically defined since there are several semen parameters which may have biological relevance.

Testosterone has not been shown to be a definitive predictor of testicular pathology or reproductive malfunction - most studies, however, have not distinguished between free or weakly bound testosterone (which is the biologically active steroid) and testosterone bound to sex-hormone binding globulin (inactive). The investigators should consider examining both total testosterone and free/weakly bound; studies which have considered the relative predictive value of sex hormones for testicular pathology have indicated that follicle-stimulating hormone has perhaps the most predictive value--albeit weak.

The investigators should consider (1) the feasibility of conducting any sex hormone analyses at all since past studies do not suggest they are of great value and (2) if hormone analyses are included, follicle stimulating hormone and luteinizing hormone should be added since they also play important roles in the interactive relationships among the hypothalamus, anterior pituitary and the testis.

A resting and step-electrocardiogram is proposed. It is hard to understand what would be identified from the electrocardiogram in this age group that could possibly be related to agent orange, nor the value of a simple exercise using a stool done in many centers in the United States.

A renal screen is proposed, based on doing a simple urine analysis. It is unlikely that this would yield any useful information. Perhaps a dip-stick for protein would show something but a tremendous number of men in this age group will have protein in their urine early in the morning.

A series of measures are proposed for liver function, which also are essentially crude and unlikely to yield any useful information. Urinary porphyrins might be of interest because of the possibility of porphyria related to agent orange, but it would obviously make much more sense to look for patients with porphyria and determine whether they had been exposed to agent orange.

The blood counts, again, offer no hope of any useful information.

Spirometry is proposed. It is unlikely that routine FEV, and FVC, considering the tremendous effects of cigarette smoking, and other environmental factors, would be of any use.

V. Comments on Neurologic Examination

Under tone, how does one include subtypes, such items as cogwheeling, etc.?

Strength - must quantify; should use standard 0-5 scale. Peripheral neuropathies involve most distal muscles; therefore, must examine intrinsics of hand. Distal wrist extensors is fairly specific for lead neuropathy. In foot, extensor digitorum brevis (forms toes) is distal muscle usually affected first in peripheral neuropathy.

Abnormal Movements - What does the grading system (1-4+) mean? It should be tabulated in the same fashion as the reflex responses.

Mental Status - How can this be left open ended? A standardized mini-mental is one possibility. It would be very difficult to grade an examiner's subjective remarks.

Even when dealing with trained neurologists, each does the exam differently with grading systems dependent on his place of training.

On page 55, under nerve conduction velocity, the sural is the only sensory measurement listed. Considering that even in toxic neuropathies which are predominantly motor, the sensory nerves may demonstrate electrical abnormalities first, both the ulnar and peroneal sensory latency and amplitude should be included. Amplitude is an important measurement since it reflects the number of axons involved in the action potential. Toxic neuropathies are usually axonal and therefore may demonstrate disease with a decreased amplitude before prolongation of the distal latency. Also it should be noted that the sural nerve may be congenitally absent.

If electrodiagnostic abnormalities are found or clinical evidence of a neuropathy is present, conduction measurements should be extended to the median and posterior tibial. This will help differentiate entrapment neuropathies from polyneuropathies.

ATTACHMENT C

AGENT ORANGE STUDY PROTOCOL REVIEW

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ATTACHMENT D

AGENT ORANGE STUDY PROTOCOL REVIEW

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April 12, 1982

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PREVENTIVE MEDICINE
AND BIOMETRICS

TEACHING HOSPITALS
WALTER REED ARMY MEDICAL CENTER
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12 April 1982

Barclay M. Shepard, M.D.
Special Assistant to the Chief Medical
Director for Environmental Medicine
Room 848
Department of Medicine and Surgery
Veterans Administration
Washington, D.C. 20420

/Barclay
Dear Dr. Shepard:

Enclosed are my comments on the latest UCLA protocol.

In response to your letter of 24 March 1982, clearly the confidentiality of the study and the confidence of the Veteran's organizations may vary in inverse relationship. My opinion is that the latter consideration should be prime. The final goal of this study is to provide the best possible assessment of the health effects of Agent Orange in a convincing manner. Rigid adherence to objective, scientific methods are essential since the study will be subjected to intense scrutiny and criticism. However, the final forum to decide its persuasiveness will not be a disinterested peer review session; it will be in the popular press and political arenas. Intuitively it would seem that a scientific study shrouded in secrecy for fear of veteran bias, funded and controlled by the Veterans Administration, and already viewed as slow, expensive, and difficult would be a poor means of persuasion. Strong scientific evidence, (e.g., tobacco vs. health) will not convince policy makers if some members of a dispute are not willing to accept the results. Therefore, all possible methods in study design that will avoid bias but maintain openness should be exhausted before resorting to secrecy.

The way to make this study persuasive is to have the confidence of the veterans' representatives that at least this is a fair, objective study of the problem. Veterans' representatives should participate in the overview of the study and be assured of its objectivity and fairness. Unlike the protocol authors, I think the Veterans Administration can direct the study and use VA facilities if the veterans' representatives can attest to study fairness.

Another "cost" of strict confidentiality is to lose a broad base of critique that can be received through an open review process. Useful suggestions could come from the general scientific community who also may become skeptical if they perceive the secrecy as unnecessary.

The benefit, on the other hand, is said to be the avoidance of bias. However, one of the advantages of cohort studies is that it is rather hard to bias objective outcome variables (mortality, documented malignancy, etc.) since the exposed/non-exposed status is already determined. Bias is much more of concern in retrospective, case-control studies. Bias in a historical cohort study might occur in more subjective complaints if an individual knew he was exposed. If he is blinded as to his exposure status, however, then subjective overstatement would be a random variable and not a source of bias. The key concern then should be security of exposure status and not secrecy of outcome variables. If a neutral agency such as Mr. Christian's office were to generate a list of names from high and low risk groups so that he alone knew the exposure status, bias would be very unlikely. He could follow a sampling process defined openly by the study advisers and all subsequent outcome measurements could be freely reviewed.

In summary, the cost of secrecy could be confidence in the study by veterans and policy makers and a limited review by even interested members of the scientific community. The benefit seems questionable at best. I would favor a variation of your question three. An independent small group of scientific consultants (particularly chronic disease epidemiologists and biostaticians) should review this question of bias on a one time only basis. If they agree with my assessment, subject the protocol to full open review. If they do not, at the least you will have an independent appraisal of the benefit and can then hire lay consultants to assess if the cost would render the study useless or present it in closed session to the advisory committee as in option 4.

Sincerely,

Dick

Richard A. Hodder, M.D., M.P.H.
COL, MC, USA
Director, Division of Epidemiology
Department of Preventive Medicine
and Biometrics

Review of Agent Orange Protocol

Per your request, I have reviewed the new "Protocol for the Epidemiologic Study of Agent Orange." More specifically this is the study of former U.S. ground troops who served in South Vietnam for evidence of long-term health effects from exposure to Agent Orange.

Referring to the critique of the earlier protocol submitted on 6 November 1981, it is obvious that the authors responded to most concerns raised at that time. This is a true protocol with a well-defined, general approach and specific details on the practical issues. The proportionate mortality study and registry review which complicated the first protocol are deleted and assumed to be the responsibility of the Veterans Administration. The new protocol restricts itself to designing the historical cohort study (and its pilot). Considerable attention is given to the crucial definitions of exposure and outcome (including possible confounding variables) although the key points by which to judge the latter are omitted from my draft. Criteria for labeling subjects as "exposed" or "unexposed" and excluding others from the study are presented. Further, there is a detailed presentation of the data collection and processing steps that are so important in a study of this size. Such specifics as tracing and contacting routines, observer and examiner training, questionnaire administration, quality assurance, "double blinding," computer hardware, data base software, sample size determination, and statistical analysis of the data are presented in good detail. This careful presentation of the materials and methods is crucial to review a protocol. It is also essential to evaluating the need for a pilot study.

I agree with a historical cohort study if exposure can be adequately documented. The starting point is to define a "cohort" of men exposed to the suspected toxin and a cohort of "controls" or "non-exposed" comparable to the exposed in all variables except contact with the toxin. What remains to be seen, however, is that this exposure can be defined with adequate confidence and at reasonable expense. As noted on page 23, direct individual exposure cannot be calculated or confirmed. One can only estimate the "likelihood" of exposure from existing records of herbicide use. The protocol would identify men and create an index for each man based on the day-by-day location of their company headquarters and the intensity of herbicide use in that area. If a broad spectrum of risk is found, the investigators will select only those at high and low extremes to effect as clean a separation of cohorts as possible. Given the surprisingly good records on herbicide use and a broad range of exposure, this should provide a reasonable enough estimate of exposure to justify a pilot study.

There are some issues in the exposure index, however, that need further consideration. First, what is the best epidemiologic sampling frame. It is expensive to identify a large number of individuals from a list of all who served in RVN and then trace each to characterize his exposure. This demands characterization of a large number of military units, often for only one individual. At least the pilot study could define exposure in a limited number of battalion-sized units and then sample individuals from units with high and low exposure histories. This should greatly reduce the amount of record searching. Care should be taken to exclude units who knew their exposure status (e.g., Agent Orange handlers, units that had spillage, etc.). Perhaps in the definitive study, a larger number of units may then be advisable in order to minimize the chance of a leak about exposed versus

unexposed units. Some attempt to validate use of company headquarters as an estimator of the soldiers position should be made in the pilot. Are there units (e.g. LRRPS) that should be excluded for this reason? Also, since officers would be more likely to be at headquarters one might reexamine the choice to exclude them if they only served one tour.

Another concern is how to use veterans' comments on Agent Orange exposure. On one hand, it will be interesting to see how accurate their perceptions are as an indicator of subjective reporting bias. However, to use it as proof of undocumented Agent Orange use would require strict criteria and if it were felt likely, people from that unit should be excluded.

The characterization of outcomes in the protocol can only be evaluated in general. The authors of the protocol are again very concerned that subjects be "blinded" about outcome variables to prevent bias. Actually, I think the key is to "blind" the exposure indices rather than outcome variables. If a person does not know his exposure, he does not know if exaggeration of symptoms will help or hinder what he wants the study to show. If he is non-exposed, false symptoms only decrease the difference between his group and the exposed. Therefore, it is much more important to maintain rigid security on exposure status. Also, the large number of variables listed in the pilot would make it hard for a veteran to be selective in his bias unless he were carefully coached. Newspaper or routine press accounts would not give enough data to overcome the internal checks that should be built into the system.

Although I can not comment on the outcome variables measured in the questionnaire and physical exam, I can comment on the methods of defining, collecting and analyzing them. On first glance, one is impressed with the

meticulous detail of the data collection and analysis system. Data will be carefully collected with multiple back checks for quality assurance. Lacking definite outcomes (e.g., specific diseases), a broad range of variables both continuous and discrete are to be measured. In essence this means the pilot study will both test the system feasibility as a pilot should, plus act as a "fishing expedition" to look for a hypothesis or a lead to follow up. I assume the extremely detailed data collection is only meant for the pilot study and then a more focused data collection effort can be undertaken. Otherwise, it would be very expensive and be easy to get lost in details or spurious associations from multiple comparisons. For completeness, it would be nice if more commentary was given on how data from the pilot study could be analyzed to generate hypotheses. Also how would problems such as non-comparability of exposed and non-exposed cohorts be handled. However, the authors do have statistical consultation to assist them and they give a good presentation of their statistical estimates.

The following are some specific comments on other points in the protocol.

1. Starting on page 52, a list of conditions to justify lab tests is given. However, these are based on acute exposures and animal models. It should be more useful to bank sera for later use and do a limited screening battery.

2. The language in the contact letter should be written at a more universal level. Words like "ascertain," "selected," "participation," etc., should be replaced with simpler words and phrases.

3. The choice of an alpha level of .01 (page 108) is selected due the "expense of the study and seriousness of the questions to be answered dictate a high degree of certainty." However, this could be construed as weighted against the veterans' chances, especially in the pilot study. Here is

clearly where Veterans' representatives input' would be important. If they demand more sensitivity, it should be stated now before Congress decides on funding rather than later when they reject the finished study because it was not sensitive enough.

A final consideration which remains is that of who should do the study. The authors feel the Veterans Administration might lack credibility with the veterans and also question the use of VA facilities. However, the controversy over the protocol as well as comments before the California legislature make the UCLA group also suspect in the veterans' view. Perhaps the VA follow-up agency and Mr. Christian's department would be the best suited for the study. Clearly an independent overview committee with veterans' representation and a neutral coordinating committee are essential. Also Privacy Act restraints that restrict access to DOD and Veterans Administration records must be considered. If an outside agency (e.g., a university) wanted access wouldn't each individual in the study need to be asked for permission before his record was abstracted?

UCLA - April 25, 1982

UNIVERSITY OF CALIFORNIA, LOS ANGELES

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SCHOOL OF PUBLIC HEALTH
LOS ANGELES, CALIFORNIA 90024

April 28, 1982

Mr. J.R. Ryan
Contracting Officer
Office of Procurement and Supply
Veterans Administration
Washington, DC 20420

Dear Mr. Ryan:

Enclosed is our revision of the Agent Orange Epidemiologic Protocol. We feel that the most productive method for handling the revisions is to incorporate the reviews and our response to those reviews as an addendum to the original protocol. In that fashion, the coordinating center will have the original protocol, the reviewers comments and our responses, When preparing the detailed place for the pilot study. Therefore, the enclosed materials include:

1) a detailed response to each of the three reviews (AOWG, OTA, VFW);

2) a veterans questionnaire, in two parts and a spouse questionnaire, revised in collaboration with the Survey Research Center of the Institute for Social Science Research, UCLA;

3) a neurologic examination form, revised in collaboration with a Professor of Clinical Neurology; and,

4) a physical examination form, revised in collaboration with a Professor of Clinical Internal Medicine.

We have considered the questions raised in your letter of April 9, 1982 and have addressed each of them in the response to the reviews. We do not favor the inclusion of a third cohort of non-Vietnam veterans and explain our reasons in the response. The limits of the study can be derived from the list of possible outcomes included in the response and from the information in the sample size section of the original protocol. Mortality information should certainly be collected on all deceased members of the cohorts. This matter is expanded upon in the response. In a cohort study such as this, the entire membership of the cohort is

established at the beginning of the study and there is no replacement of members who die, refuse etc. Death is, in fact, an outcome in this study.

Thank you for the opportunity to work on the development of this protocol.

Sincerely,

Gary H. Spivey

Gary H. Spivey, MD, MPH
Associate Professor
Division of Epidemiology

Philip Costic
Senior Contracts and Grants Officer
Office of Contracts and Grants Administration

GHS/PC:kc

VFW REVIEW

1) Basically, the VFW finds the general framework of the revised protocol quite an improvement compared to the original design and feel that once the modifications and changes that are recommended by the OTA and VA panels have been acted upon, the design should be acceptable.

We wish to thank the VFW for their careful and considered review of our protocol and for their support. We believe that the support of the VFW throughout the conduct of this study will be of the utmost importance to the coordinating center.

2) The length of time for the epidemiological study as pointed out at the February 16th OTA review, indicated that a minimum of five and a half years would be required to complete the entire study. We feel that, at this time, a specific timetable cannot be feasibly arranged. We feel that as the study progresses a deadline can be established depending on the accumulated findings and the number of participants at the various intervals of the study.

We understand the VFW point that a time table is difficult to specify at this point. However, we feel that an expected time table should be part of the protocol so that the cost of the proposed study can be estimated and concerned individuals will know when it is reasonable to anticipate results from the study. We have suggested points at which the study should be terminated, if indicated. The data cannot be analyzed in stages during data collection to make a decision as to when the study should or should not be stopped. Rather, the nature of the study design requires that all prespecified data collection be completed before interpretation of results is possible.

3) A recommendation by one of the OTA panel members was that an oversight committee be established to guide the pilot study and the operational phases of the epidemiological study. We agree that an oversight committee needs to be established, however, the VFW strongly feels that any continuing monitoring or involvement of this herbicide issue and the epidemiological study should include the VFW's continued participation. It is a well known fact that the VFW has been one of the forerunners of this issue, therefore it would not be in the best interest of those we serve to neglect or fail to continue participating as the study progresses.

The oversight committee should be privy to all details of the study design and conduct including 1) information which may be withheld from the coordinating center for purposes of blinding and 2) information which could be extremely damaging to the conduct of the study if made public. Therefore, we feel that a condition for service on this committee should be agreement to maintain the confidentiality of study data until the results of the study are officially made public. We feel that a representative from the VFW could make an important contribution to the oversight committee.

4) In our recommendations on the original design, we suggested that an independent medical school conduct the physical examinations, surveys, and complete any questionnaires that would be devised. However, in light of the new information that was brought to our attention at the February 16th OTA review, we feel that the organization known as the National Center for Health Statistics (NCHS) Health and Nutrition Examination Survey (HANES), seems to meet our criteria of proper credentials and independence and should be considered as should any other similarly qualified contractor.

We agree.

5) The Veterans of Foreign Wars has long been involved in seeking a fair and expeditious solution of this issue and would certainly be most happy to assist in publicizing the conduct of the future study and encourage Vietnam veterans' participation.

We certainly believe that the cooperation and assistance of the VFW in publicizing the study should be sought and encouraged. The assistance of other veterans groups may also be similarly sought. Such cooperation may very well make the difference between success or failure of the study.

6) We find ~~it~~ hard to believe that the designer of this study feels that it is unnecessary to include officers as well as multitour enlisted men. It is inconceivable that officers were immune from the same conditions or maladies suffered by the enlisted man. We therefore feel there is no basis for such an exclusion. The designers should be reminded that the purpose of this study is to determine exactly where the individual veteran served, the type of herbicides to which he was exposed, and the amount of that exposure. The final question that needs to be answered (regardless of rank or numbers of tours of duty in Vietnam), is: the relationship between the exposure to these herbicides and the disorders being claimed by individual Vietnam veterans.

We would like to clarify our position in regard to officers and multiple enlisted men. We did not intend to imply that inclusion of officers or multitour enlisted men is unnecessary. Our feeling is that such a group cannot be included in a valid fashion unless a comparable group of exposed and unexposed officers and multitour enlisted men can be identified. We are in complete agreement with the OTA reviewers that a final decision on this question should be reserved until the cohort selection procedures have been completed. At that time it will be clear whether or not an appropriate comparison group can be identified. Unfortunately if an appropriate comparison group is not identified, any findings in the officers and multitour enlisted men could not be easily interpreted.

7) The VFW is aware that the examination which will be utilized in the epidemiological study was modeled after the Australian government's own study. However, as has been suggested by us and others, changes need to be made on the physical examination and must be implemented in a manner that is suitable and recognizable to the examining physician as that of a standard "Americanized" examination physical. In stating that the exam needs to be "Americanized", one only needs to compare the definitions, classifications, and scales used in the proposed physical examination.

We are not sure what is being referred to in the physical exam form as being not standard American practice. This physical exam form has been reviewed by several American trained physicians who have not identified any area needing Americanization.

8) Some panel members feel that an incentive factor should be included in this study to encourage participation in the examination and interview process. It is apparent that based on past cooperation by the Vietnam veterans and their willingness to participate in the Veterans Administrations Agent Orange examinations (which to date have totaled approximately 53,000 examination), that a distinction needs to be made between incentives and compensation factors. We do agree that a compensation factor needs to be considered, especially in light of lost wages, travel expenses and other incidentals that would be incurred through a veteran's participation. Consideration should be given to a compensation formula similar to that being used by the Air Force's Kelsey-Seybold contract to study personnel who participated in Operation Ranchhand. With regards to the different cohort groups, special attention should be given to maximizing participation by the non-country Vietnam Era veteran. Thus, proper compensation for their time must be a consideration, but certainly in the interest of equity, so should it be for all veterans participating.

The question of compensation and incentive pay is extremely difficult. We believe the question of compensation must be examined in the pilot test considering issues of ethics, practicality, costs and experience of other current studies. We certainly feel that any out-of-pocket expenses for travel, lodging and meals during the time of the scheduled examination procedures should be fully compensated. It might be appropriate to compensate the individuals for lost wages during this time period, but this could increase the cost of the study significantly. Alternatively, since this study is congressionally mandated, it might be possible to have the Congress legislate a practice of granting the appropriate amount of time-off with pay by the employers. A final point is that whatever compensation is provided must be done in a uniform and equitable fashion for all participants.

Selection

The panel unanimously agrees that the Department of Defense (DOD) should select the cohorts in accordance with Dr. Bricker's cohort selection paper (Tab A). This will provide, we believe, for elimination of as much misclassification as is possible from the existing or potentially reconstructable records. We believe it is absolutely essential that the identification and assignment of these individuals to the different cohorts not be available to the participants or to the investigators until initial analysis of the data is completed. The Science Panel will oversee this cohort selection process. The study investigators must be aware of the method used to select the cohorts but must not be aware of the individuals placed in each group.

We recommend pilot testing the cohort selection procedure outlined in the proposal developed by Dr. Bricker along with our proposed procedure. We derived our own proposed mechanism for cohort selection taking into account the proposal submitted by Dr. Bricker. The major difference between the two proposals is that Dr. Bricker recommends assigning individual likelihood of exposure levels on a group basis whereas our proposal calls for an individual calculation of exposure likelihood. We believe that with the high rate of personnel turnover in military units in South Vietnam, the classification of individuals according to the exposure likelihood of their unit without examination of the actual time period of that individual's presence in the unit could lead to serious misclassification. This question should be examined in the pilot study. If serious misclassification is not encountered then we would certainly support the less costly procedure proposed by Dr. Bricker.

We disagree with one procedure suggested in Dr. Bricker's proposal - the proposed validation of exposure status by use of the Agent Orange registry. Dr. Bricker suggests that if the exposure likelihood assignment is correct, a high proportion of name matches from the presumed highly exposed battalions to individuals in the Agent Orange registry should be found. This procedure is based on the assumption that high exposure did in fact cause health problems that would lead an individual to report to the Veterans Administration for inclusion in the registry and/or that the individual had sufficient knowledge of the fact of his exposure to lead him to report to the registry. Either of these assumptions could be incorrect. Therefore, any lack of "validation" by this method would have no meaning. In addition, the individuals who have filed claims through the Veterans Administration are not a scientifically selected group, but are a self-reporting group. We feel strongly that abandoning the selected cohorts or the currently proposed protocol on the basis of "non-validation" from use of the Veterans Administration Agent Orange Registry records would be a serious error.

We endorse the suggestion of the Agent Orange Working Group that the investigators from the selected coordinating center should be blinded (until the analysis phase) as to the actual presumed exposure status of individuals selected for this study. We believe that the coordinating center investigators, however, must be involved in developing the mechanism of selection of the study cohorts and in particular must be involved in the determination of comparability of the proposed high and low likelihood of exposure cohorts and any non-Vietnam cohort. This can be accomplished, while maintaining blinding, by involving the coordinating center in the development of the criteria to judge comparability, and by providing them with the relevant information to judge comparability but with any unit identifying information suppressed.

We must point out that while it may be very desirable to blind the coordinating center as to the exposure status of the study participants during the data collection phase, the coordinating center must have some kind of cohort identifier prior to the beginning of analysis. It would be impossible to do meaningful analysis without being able to separate the study participants into their respective cohorts. The analysis could, however, still be done blind by providing the coordinating center with the individual assignments to their respective cohorts but identifying the cohorts only as "A" or "B". To assure that information will not be lost, the inclusion of one or more deeply encoded cohort identifiers (group A, group B) might be imbedded in the identification number. The code on such identifiers would not be broken until the analysis phase.

Criteria For Each Group

We recommend that groups be composed of high probability of exposed Vietnam veterans, high probability of nonexposed Vietnam veterans, and a non-Southeast Asia veterans group. Some felt that it would be desirable to include a Vietnam veterans group exposed midway between the first and second groups in order to make an assessment of dose response. The consensus is that though this may be desirable, the inclusion of the fourth group is not essential nor critical to the study.

We continue to have reservations about the ultimate utility of a non-Vietnam service cohort. However, if such a cohort is to be included, we strongly recommend that consideration be given during the pilot study to the use of those units which were scheduled to be sent to South Vietnam but which, at the last minute, were not sent. We feel that these groups would be more likely to provide a comparable cohort to those serving in South Vietnam than would the use of all troops from the southern part of the United States (as suggested in Dr. Bricker's proposal).

We feel that the comparison of a non-Southeast Asia veterans group with combat veterans would be very difficult to interpret because of the different selection biases related to area of service. In addition combat veterans represent survivors whereas the non-South Vietnam veterans do not. Also, the use of this extra cohort with all of its problems in interpretation will add considerably to the cost of the study.

Proposed Exclusions from the Cohort Group

We believe it is unreasonable to exclude officers and multi-tour Vietnam veterans. These may be separately identified so that appropriate analysis can take place but they should not be excluded from the study.

We recommended in the protocol that the officers and multitour enlisted men be separately identified. Meaningful analysis of this group, however, can be done only if there are appropriate comparison groups. Whether or not both high and low likelihood of exposure groups can be identified will be clear by the completion of the cohort selection procedure and at that point this question can be reconsidered.

Questionnaire to Personal Health Providers of the Individual Veterans

Some of the selected veterans may have had multiple health care providers since returning from Vietnam. The panel doubts that many private physicians will fill out detailed questionnaires on their patients and thus wonder about the usefulness of this part of the study. The needed information may have to be obtained in other ways.

We understand the Working Group's concern about whether private physicians will respond to questionnaires on medical record validation. We can point to the experience that we have had in the Health Status of American Men project which has undertaken validation of medical records on approximately 20,000 men. The physician non-response rate in this study has been less than 10%. Thus, we have no reason to believe that this would be a serious problem for the Agent Orange study. In addition, we know of no other mechanism by which medical record validation could be achieved. We expect that the number of veterans who will have sufficient Veterans Administration records for validation purposes will be small. Furthermore, such a group would be unlikely to be representative of the total cohort.

Individual Veteran Questionnaire

The questionnaire as it now exists is unacceptable. It is overly long and uses highly technical terminology which many people including many physicians will not understand. We recommend that careful thought be given to the information that is needed to be gathered, who will administer and where the questionnaire will be administered (telephone, home visits, etc.), and that the questionnaire be redesigned to meet those criteria. The questionnaire should be limited to information that is critical to the study and that will be used in the analysis of the results.

The questionnaire in the proposed form is, admittedly, too long. We have now separated the questionnaire into a section which includes demographic information, Vietnam exposure information and the majority of the potential confounders. The second section of the questionnaire is the medical history section. Each of these questionnaire segments should take about an hour to complete and since they can be done in separate sessions, should be perfectly acceptable to the veterans. Separating the medical history section from the questions on Vietnam experience should further help to reduce potential bias from tying the two together. We specified in the protocol and will reiterate here that the questionnaire must be administered by a trained interviewer at the appropriate examination center. We feel strongly that the questionnaire should not be administered in the home or any other location prior to the veterans' attendance at the examination center. The primary reason for our concern is that the use of such a two stage procedure would greatly increase the probability of dropouts between the administration of the questionnaire and the conduct of the physical examination. The questionnaire has been carefully reviewed and we believe that all information included in the questionnaire is potentially necessary and should be pilot tested. We have also revised the questionnaire to avoid the use of unnecessarily technical language.

Other Instruments

The psychological and neuropsychological instruments, all of which were not available for review, should be evaluated and should include only information that will be used in the analysis of the results and presented in a way that would not be offensive to the participants.

We certainly concur that neuropsychological and psychological test batteries should not be offensive to the subjects. These are standard test batteries which have been widely used and accepted by a wide range of subjects.

Physical Examination

Data collected from the physical examination should be limited to those items that will be used in the analysis of the study. This does not mean that the physcial examination should not be comprehensive as determined by the examining physician for the particular individual, although items to be used for analysis of results must be collected according to a standard protocol.

The examination procedures were chosen to include items that can be used in the study. These procedures are almost entirely standard procedures that would be conducted during a physical examination in any event. The length of the form reflects the fact that we have required a specific checkoff of conditions which would generally only be noted if they were found on physical examination. Such a checkoff list is necessary to insure standardization and can be rapidly completed. The examination protocol has been revived by a professor of medicine at UCLA and, in his opinion, conforms to standard American medical practice.

Laboratory

The final decision for the inclusion of laboratory tests for this study should be made after consultation with laboratory scientists to ensure that the best tests for that particular purpose are being used. There are other tests such as chest x-ray, spirometry, nerve conduction tests, etc., that probably have limited usefulness because of the inability to standardize and to intrepret between multiple examining centers.
It is critical that the standardization of laboratory procedures proceed with quality control and quality assurance for collection, transportation, handling, and analysis and that this process be begun immediately in the participating laboratories.

We certainly agree that some tests such as spirometry and nerve conduction would be difficult to standardize between multiple examination centers. However, the varability between centers could be evaluated within exposure groups. The utility of these tests, and particularly the ability to standardize their application, could be examined in the pilot study.

Other Areas of Concern

For all participants, the panel believes that information should be collected only on those items that are critical to the study, can be standardized, and are such to appropriately interpret between multiple examining centers and laboratories. If the practising physician feels that additional information is necessary for a particular patient to evaluate the health status, it obviously should be done but should not be part of the overall data collection and analysis for the purposes of this study.

Certainly if the examining physician feels that additional information is necessary to evaluate a particular participant, he or she should be free to do so. However, at a minimum, the standard protocol must be followed to insure standard collection of data.

It is not clear from the proposed protocol the duration of the overall study or time estimates for each individual participant. These should be determined. A possibility that should be considered in regard to future duration is that after completion of the initial examination and analysis, the cohorts names be matched against the National Center for Health Statistics (NCHS) Annual Mortality Index. This would provide nearly all of the necessary followup information and would be more efficient than a mail survey or a hands-on followup of each individual.

The duration of the overall study was specified in the timetable section of the protocol. The duration of the examination time for each individual participant is more difficult to estimate at this point. It certainly could be expected to take at least two days. More accurate estimates can be developed at the completion of the pilot study.

We support the suggestion that future follow-up be accomplished, if possible, through the use of the National Center for Health Statistics Death Registry. However, it must be kept in mind that not all states participate in the death registry and the impact of registry incompleteness on follow-up must be ascertained in a pilot study. In addition, we suggest that future consideration be given to the possibility of actual re-contact of subjects for evaluation of non-fatal illnesses which may be of potentially serious concern to the veterans.

After the initial analysis has been completed and depending upon the results, additional well focused, smaller studies, such as specific case control studies, may be necessary to further define the extent of possible uncovered problems.

After the initial analysis has been completed, the method of cohort selection should be made public. While still ensuring individual confidentiality, each participating veteran should be informed of his or her status in the cohort selection process.

We certainly would support the suggestion that specific case-control studies or other such relevant studies be conducted after completion of base-line analyses from this study. Also, at that time the method of cohort selection and/or the full protocol can be made public and participants informed of their presumed exposure status as determined by the study.

It should be explicitly stated in the final design that when an abnormality for an individual is found, how that abnormality will be followed, who will follow and treat it, and what system will be set in place to ensure that each individual will receive the necessary medical care.

The panel suggested that we specify a mechanism for insuring appropriate follow-up for individuals found to have abnormalities at physical exam. The basic mechanism for follow-up of these abnormalities is provided in the protocol draft. Any necessary adjustments to this procedure to guarantee its practicality and workability should be made on the basis of experience from the pilot study. (See also comments in next section.)

The panel assumes that the final protocol will address the usual concerns of patient confidentiality, freedom to withdraw from the study, and methods of providing the individual veteran specific medical information of which he or she or his or her physician should be aware for the proper care of the individual veteran.

<u>Confidentiality.</u> This involves knowledge of an individual's participation in the study, connection of the individual with results of the study, and reporting of results to others. The first should be managed by maintaining limited name and address card files, with encoding for fact of participation, available only to study staff working directly with records. No inquiries about participation, not authorized by the participant in writing, should be answered other than with a form letter stating that all such inquiries concerning participation must be made to the possible participant.

Segregation of identifiers and data, can be handled with removable identifiers and reencoded identification numbers for data from different sources. However, straight or encoded initials for error checking should also be incorporated. No data forms should have identifiers left on them. Cover pages with identifiers should be filed separately. Computer records should be maintained without identifiers and the connection between data and identifiers, if needed for information checks or notification of participants, should be made by specially trained staff.

Data collected in the study on any individual should not be made available to any third party without the express written consent of the participant. All analyses should be reported in statistical terms; any anecdotal reporting and/or reporting on individual or very infrequent findings, should be made with sufficient alteration to protect the individual's identity while preserving the information.

Freedom to Withdraw. The informed consent form should include a statement about freedom to refuse to participate in the study and freedom to withdraw from the study at any time without prejudice. It will be particularly important to reassure the veteran during recruitment that his status with the VA and his access to VA benefits is not affected by his refusal or withdrawal. The freedom to withdraw should probably be reiterated at each major contact, especially if the study contacts are at VA facilities.

Notification. Notification (methods of providing the individual veterans with specific medical information concerning their proper care) can be handled in three ways (see also the discussion in section III.B.13 of the protocol):

a) The physician responsible for the initial examination should be allowed, at the end of the exam, to discuss findings, especially any findings needing urgent follow-up, and to recommend such follow-up to the veteran. A similar mechanism should be set up for immediate notification concerning laboratory findings requiring urgent follow-up. There should be later follow-up from the study to assure that appropriate medical attention was obtained.

b) Reports of findings should be sent to the physician or medical care entity designated by the veteran at the time of the examination. The report should include findings, notation of abnormal findings and some recommendation for follow-up, if necessary. The veteran should be notified that such a report has been sent. If the veteran has not specified a health care source, and if there are not notable problems, he/she could be advised that such a report is available to be sent if requested later. If there is need for follow-up, the veteran should be urged to contact a health care source to which the report can then be sent.

c) A specially prepared report and interpretation of findings could be sent to the veteran. This could be based on the computerized reports sent out following screening examinations or health risk appraisals by companies such as Cardio-scan or General Health. In these, the findings are reported and reviewed in terms of range of normality or abnormality, and appropriate actions, if any, recommended in terms of health care, habits and future activities.

Pilot Study

We believe the Pilot Study should include 5 percent of the anticipated study population. We recognize it may not be possible that this be a random sample of the population but that it be clearly stated and understood what that 5 percent represents. The panel unanimously disagrees that the Pilot Study should take place in only one study site but recommends strongly that it be conducted in all examination centers and study sites that will be used in the overall study. The Pilot Study should be used to determine participation rates and to further refine the instruments to be used in this study. An analysis of the results of the pilot study can be used to make a determination of the possibility of success of the larger study. The results should in no way be interpreted as to effects but only whether it is possible to conduct a scientifically valid overall study.

If cohorts of 6,000 veterans are identified, the proposed sample size for the pilot study of 5% of the cohort will be larger than recommended in the protocol. If cost is not a factor in the decision we would agree with the panel. However, we feel that a sample size of 400 subjects would be adequate.

We believe that the 400 subjects (or 5% of the study cohorts) selected for the pilot study must be a random sample of the different cohorts. Otherwise, conclusions from the results of the pilot effort will be very difficult to interpret.

We understand the panel's concern about conducting a pilot study in only one examination center. We, however, do not agree that the pilot study should be conducted in all potential examination centers as the mechanics and cost of the pilot study would be very much increased. In addition, because of the small number of subjects that would be anticipated in any given examination center, we anticipate that the results might be more confusing than helpful. We would support the recommendation of the OTA review panel that two or perhaps three examination centers be included in the pilot test. This would allow for examination of problems of coordination between centers but would keep the pilot study within a more feasible range of effort.

Optimism about the protocol and the study was not universal among the OTA Advisory Panel members. Some panel members, while commending the UCLA team for their industry in writing a protocol of this complexity and their ambition in the scope of their proposal, expressed great reservations for the project. These feelings represent a lingering disagreement about whether such a study should be done at all, and to a lesser extent whether the current protocol is adequate to the task. The pessimism stems principally from two sources: the undeniable fact that the investigators are proposing to embark on a very general search for disorders of various organ systems, and the circumstance that exposure to the agent was at variable dosage levels and took place between 10 and 15 years ago. In view of such reservations it is important that the investigators clearly describe the limits of the study, and that the decision to continue be based on estimation of the kinds of health effects detectable by the study.

> The limits of the study in terms of detection of health effects are provided in general terms in the protocol section on sample size. Outcomes of any given frequency can be compared to the recommended sample size, utilizing the figures in that protocol section. We have attached to this addendum a table (Table I) which includes effects which have been noted in animal studies, effects which have been noted in human studies, and our guess, at this point, as to the most likely possible effects to be seen in humans based on the combination of animal and human evidence. This list includes items such as reproductive effects which we do not consider likely but which we feel must be included in this study.

2. Timetable

An overall study length of five and a half years, divided into two and a quarter years for development and pilot testing, two and a quarter years for implementation of the full protocol and one year for data analysis is proposed. The division into stages is appropriate and the initial stage is about right in length. However, the implementation and analytical stages appear overly optimistic, allowing little or no time for enrollment, scheduling and the general milling around which is the inevitable concomitant of any large, complex, multi-institutional study. An overall length of at least 7-1/2 to 8 years seems a more reasonable planning horizon for this investigation. Time estimates can be refined as planning progresses.

We agree with the comments.

3. Checkpoints

The investigators have identified a number of points at which progress should be evaluated and the study halted if certain criteria are not met. OTA endorses such step-wise decisionmaking and cautions only that the criteria for making decisions concerning continuation must be stated clearly in advance.

Obvious checkpoints involve several issues discussed in this review. For example, early in the detailed study design the following questions must be addressed:

1. Can troops be successfully assigned to high or low likelihood of exposure categories?

2. Are there sufficient numbers of troops in each cohort to carry out a meaningful study?

3. Are the endpoints to be examined sufficient to justify executing the study?

A negative answer to any of these questions should result in calling a halt to the study and a rethinking of possible approaches to learning about possible health effects from Agent Orange.

We agree

4. Oversight Committee

The proposal that an oversight committee of eminent scientists be empaneled to guide the pilot and full operational phases of the study is excellent and should be adopted without question. Representation from one or more of the veterans' organizations also should be considered. Such a committee will provide a buffer for an investigation of great public and personal sensitivity. The committee should be appointed as soon as possible, to be available during planning for the pilot study and to play a key role in the "checkpoint decisions" of whether to proceed through the stages outlined in the protocol.

> The Oversight Committee must have access to all pertinent information regarding the design and conduct of the study including the details of exposure estimation and endpoint determination. The members of the committe, therefore, must be sworn to absolute confidentiality concerning all aspect of the study. We agree that the committee should be appointed as soon as possible and, in fact, feel that it should be in place even before the selection of the coordinating center. A representative from a veterans organization may be very helpful on this committee.

5. Pilot Test

The investigators propose an overall pilot test of 2-1/4 years involving 400 participants and a single examining center. The time allotted for and size of this investigative phase seem appropriate. However, the choice of a single examining center, though defended, may be unwise. Lack of standardization and comparability between centers will be one of the most difficult problems in the full study. To conduct a pilot study which provides no information in this area would be regrettable. At lease two pilot centers should be identified.

> We agree that two or three examining centers would be valuable. We do not recommend more than three. (See comments from AOWG review section.)

6. Limits of the Study

Before pilot testing can begin, the limits of the study must be clearly drawn. Statistical probability dictates that, for a study of any size, no matter how perfectly designed, effects occurring with low frequencies, as a result of an exposure, may, by chance, not be observed at all. The ability to detect effects at lower and lower frequency increases with the number of participants, but there are always limits.

These two limitations, that imposed by a limited number of participants and that of limited ability to infer causation, are both pertinent to the proposed ...dy. The total population of Vietnam veterans is finite, and very rare events ...uch as certain malignant tumors at these young ages may be undetectable because of sample size, even if they are strongly associated with Agent Orange exposure. On the other hand, some common effects may indeed be due to Agent Orange, with only a slightly increased frequency. In these cases, large numbers of exposed subjects may experience the effect, but it will also be seen in large numbers of non-exposed men. Even if a difference is demonstrated and with the large numbers of cases is highly significant, it cannot be assured that the excess is not due to some initial vulnerability of the exposed.

A different limitation of this type of study is that of determining causation. Even if a study is sufficiently large to be clearly significant statistically, it is at times impossible to conclude that an excess of effects seen ...n exposed subjects is caused by the exposure studied. The alternative explanation ...st be considered that the exposed subjects were a more vulnerable group initially and would have experienced the effect more commonly whether or not they had been

sed. This problem cannot be solved by including large numbers of subjects, even if very large numbers are available for study. The problem can be alleviated if it is possible to study the subjects carefully and to determine that they were not initially different in any important way. If there is a strong association between exposure and effect, and if the two groups seem to have been generally similar before exposure, it is reasonable to conclude that a large effect is probably due to the exposure. But if the association is weak, so that the effect is only a little more common after exposure, it is generally impossible to be assured that some minor initial difference between exposed and not exposed is not the true cause. The requirements here are both adequate number of subjects and adequate strength of association.

Probably the main strength of the study is that it will provide upper estimates the magnitude of each endpoint for which analysis is carried out. Upper estimates will be available even for rare diseases and diseases weakly associated with exposure. But only for diseases sufficiently common to occur in large numbers and which are also strongly associated with Agent Orange will clear demonstration be possible that the disease is due to this exposure. There may be no such conditions identified.

> Utilizing the sample size determination section of the protocol, the probability of being able to detect a difference between high and low exposure groups of any given magnitude or a condition of any known frequency can be determined. It is certainly clear that the study would be highly unlikely to detect rare events such as soft tissue sarcomas in a study of this size. The determination of whether the detected effect is most likely due to the exposure or some other factor is a central part of the conduct of any epidemiologic study. The procedures for handling this problem are specified in detail in the study protocol sections dealing with selection of study groups and confounding. The initial selection of the high and low likelihood of exposure cohorts must be very carefully done to ensure comparability of these groups. We feel that it is mandatory that both the coordinating center personnel and the Oversight Committee be heavily involved in this process.

7. Structure of the Study

The investigators have suggested a number of procedural mechanisms to be considered as the details of the study are developed. These basically concern responsibility for conducting interviews and medical examinations and the sites of such activities. Though these logistical aspects need not necessarily be decided in the scope of the current contract, the Panel made some suggestions. The investigators raised the possibility of using VA medical facilities to carry out the examinations. The Panel did not reject the idea of using VA facilities, but a number of concerns were expressed. Some of these issues were raised in OTA's review of the first draft protocol, and are mentioned in the current protocol. There is long-standing concern about various factors which might affect participation rates, and it may be that some veterans would be deterred from participating if the examinations were to be carried out at VA hospitals. Before any decision is taken to use VA hospitals for the full-scale study, the effect on participation should be determined during the pilot study.

An encouraging note in this regard is that, currently, about 3,000 veterans monthly are examined as part of VA's Agent Orange Registry. This participation may be interpreted as showing that veterans will participate in a study in VA facilities.

organizational structure for conducting studies already exists within the , namely the Cooperative Studies Program (CSP) which conducts collaborative clinical trials among VA hospitals. The organizational structure for each clinical trial within the CSP consists of a chairman's office and a designated biostatistics research support center (of which there are four around the country) who together coordinate the study and perform monitoring, quality control, and analysis. There is an external Operations Committee that meets periodically and reviews progress and adherence to the protocol. This background of experience in conducting collaborative research within the VA, with an organizational structure similar to that proposed by UCLA, could be valuable to the investigators in fleshing out the details of the protocol.

Aside from the possible effects on participation rates of using the VA medical .ities, the other major concern, and perhaps the more serious one, is the .oblem of standardization among personnel and procedures in the examination centers. This will be a thorny problem regardless of who conducts the examinations. The opinion was expressed and supported that it might be more difficult to achieve standardization in the VA system than in other health facilities.

A suggestion that garnered nearly unanimous support of the Panel was to consider contracting with the National Center for Health Statistics (NCHS) Health and Nutrition Examination Survey (HANES) for both the interview and the medical examinations. This program uses mobile examination facilities. The purpose of HANES is health assessment (as opposed to the treatment orientation of most general medical institutions) which is exactly what is needed in this type of study. The usual complement of HANES study personnel might have to be augmented by neurologists other specialists for this effort, but that should pose no major problem. HANES personnel are accustomed to following strict protocols, and are equipped to gather

yze biological samples. Collecting and storing biological samples might be nsidered as part of the study. If pertinent new tests become available, they can run on the stored samples.

OTA urges the investigators and VA to consider HANES or another equally ualified such group. (For a brief description of HANES see Attachment A.) egardless of the organization performing examinations, the appropriate referral ould be made for any condition requiring medical attention, whether it be to a VA facility or to the participant's private physician.

> We fully support the recommendation that a contract with the National Center for Health Statistics Health and Nutrition Examination Survey (HANES) be considered. However, we caution that the HANES personnel must be willing to revise their procedures in accord with the protocol examination.

6. Cooperation and Coordination Among the Organizations to be Involved in the Study

Beginning with the pilot stage, the Agent Orange study will involve cooperative efforts on the parts of several organizations. Aside from the review groups such as OTA, the VA Herbicide Panel, the Agent Orange Working Group and perhaps the National Academy of Sciences, attention has to be directed at the organizations that will plan and execute the study.

First of all, the VA will have to decide upon a primary contractor to develop the detailed plan, and the contractor will presumably arrange subcontracts with other organizations to administer the questionnaire and medical examinations. If the suggestion in the protocol is followed, some agreements should be made with erans organizations so that their good offices can be used to publicize the study and encourage participation in it. Furthermore, the relation between the Department of the Army, which will contribute to the exposure index, and the VA and the primary contractor will have to be detailed. The sooner the links can be made among all these organizations the better.

We agree completely with the reviewers on this point. The proper cooperation and coordination among the organizations will be essential to the conduct and completion of the study.

Exposure Likelihood Index

The contractors provide an orderly description of the steps necessary to epare an exposure likelihood index. At the same time, the authors remain properly utious about whether any index which can be constructed will have a useful degree correlation with likelihood of exposure.

During the time the investigators were working on the present protocol, Dr. rome Bricker of the Department of Defense developed a different method for nstructing an index (Dr. Bricker's scheme is included in the protocol as Appendix . Dr. Bricker enjoys and benefits from a working relation with Mr. Richard ristian who, by general agreement, knows more than anyone else about the records cessary for the study of Agent Orange exposure in Vietnam. Dr. Bricker and Mr. n strongly hold the opinion that Dr. Bricker's suggested methods would be icker and easier to use. Mr. Christian, who was at the OTA Advisory Panel eting, said that his organization could provide an index based either on the UCLA Dr. Bricker's proposal.

The UCLA protocol recommends that a member of the organization that will ordinate the study work closely with the Army in developing criteria for the posure index. For example, the cut points that will establish whether a unit is nsidered to be in the high or low likelihood of exposure groups must be defined in cooperative manner between the contractors and the Army. The protocol also commends that the Agent Orange Working Group be involved in establishing the riteria that will establish which units are considered to be in different exposure roups. These are commendable ideas.

OTA did not decide which method of constructing an exposure index was better. urther discussion and collaboration between the contractors for the pilot study and

Army and possibly the Agent Orange Working Group should lead to a decision about the preferred method. That is considered a detail best left to the designers of the study and the records experts.

> We would agree with this series of comments. However, please see the detailed comments concerning Dr. Bricker's proposal in the section in the Agent Orange Working Group review above.

a. Cohort Selection

The question of how an individual would finally be selected to a cohort based on likelihood of exposure received a great deal of attention from the Panel. There was concern that the problems of determining whether or not an individual was indeed with his company on a given day might be overwhelming. How much error would be introduced by the assumption that the entire roster of a company was present on a given day, leading to assignment of all company members to the same exposure status for that day? A test run on a few companies to determine how great a difference there would be between the group method and the individual method of exposure determination might be of value and should be considered. If the group method did not create a significant amount of misclassification (a level determined by the investigators before the test begins) the need to resort to the individual method might be obviated.

> We certainly agree that a test of the amount of misclassification from the use of a group method of exposure estimation should be made.

b. Third Cohort

About one year ago, there was a general impression that a study of Agent Orange was impossible. At that time, discussion began about a study of the "Vietnam experience" as an alternative to the seemingly-impossible Agent Orange study. Such a study would necessarily involve study of some comparison population not exposed to the "Vietnam experience," a third cohort. Since then, the efforts of the Department of the Army and the Agent Orange Working Group, with prodding from veterans organizations, have produced records that provide some assurance that exposures to Agent Orange can be estimated. That assurance, in turn, means that an Agent Orange study can be mounted. The fact that an Agent Orange study can be mounted, however, does not mean that it will necessarily produce meaningful results or clarify important issues.

The contract placed with UCLA called for the development of a protocol for an Agent Orange study. OTA, in reviewing the protocol, has restricted itself to consideration of an Agent Orange study in contrast to a Vietnam experience study.

However, the issue of a "third cohort," a group of veterans who did not serve in Vietnam, was discussed at the OTA Advisory Panel meeting. Those who favored expansion of the study saw an opportunity to answer a number of questions by including the third study group. Those opposed to expansion cited the major problem of choice of endpoints to be included in such a study. Concentrating largely on health effects expected from toxic chemicals is seen as a necessary step in refining the questionnaire and medical examinations to study Agent Orange. If the study is expanded, other endpoints more directly related to war experiences will have to be considered.

> We still believe that this additional cohort would not only be expensive but unlikely to be meaningful because of differences in selection and survivorship.

c. Officers and Multiple Tours

The exclusion of officers and individuals with multiple tours of duty, as is posed in the protocol, would be unfortunate in that these individuals may include arge proportion of the most highly exposed soldiers. The suggestion was made t such individuals be segregated from the others, but that no decision be made ut excluding them until every effort was made to include them in the study. The ficulty in including officers and multiple-tour veterans in the study arises from : fact that the probability of a multiple-tour veteran's being in the low kelihood of exposure group is very small. A comparison of multiple tour exposed bjects with single tour unexposed subjects was considered uninterpretable because c--founding factors. If that is the only comparison possible, the UCLA proposal ude officers and multiple-tour individuals should be supported.

We agree.

.0. Locating and Recruiting Veterans for Participation in the Study

The protocol thoroughly outlines steps for locating veterans. Certainly the use of IRS files to locate veterans would make the process more efficient. Permission for such use of IRS data is granted for National Institute of Occupational Safety and Health studies, and it should be sought for this study.

In contrast to the details provided about tracing veterans, there were too few about problems of recruiting the located veterans into the study. Problems with differential response rates, that is, differences in the willingness to participate among the low and high likelihood of exposure groups are mentioned, but no specifics are provided about what is to be done to improve participation. There is also a ... of discussion of the treatment of cohort members who already have died. Some ... collection procedures must be developed for those individuals.

> It is difficult to anticipate the direction or magnitude of differential nonresponse rates. A case could be made for either the high or low likelihood of exposure cohort having a different response rate. However, in order for there to be such a differential, the individuals would either have to know their status according to the study criteria or there would have to be a high degree of correspondence between their perceived status and that documented by the study. If there is no such correspondence, the differential would be unlikely to exist. We feel that maintaining strict confidentiality of the presumed exposure status of the individuals, including blinding of the coordinating center and examination centers during the data collection process, and agressive recruiting for all study participants will help to minimize differential response rates. Furthermore, if the examination procedures can be run so as to be as pleasant as possible to each participant, response rates should again be maximized. However, if a differential response rate is, in fact, encountered then a subsample of nonrespondents should be diligently pursued in order to ascertain their characteristics.

The collection of data on cohort members who have died since their discharge from the service can be a difficult problem. The death certificate should be obtained. If possible, available medical records on these individuals should also be collected. This would require consent of next-of-kin. The next-of-kin would also probably be the source of information about the existence of such medical records. However, certain things can be obtained including the military records which should be abstracted as for any other study participant and any existing VA records. If possible, it might be desirable to conduct an interview of the next-of-kin to elicit information parallel to that obtained for the live participating veterans. Our own experience in a somewhat similar study found the next-of-kin of young men extremely reluctant to cooperate in any fashion with the study. In addition, the next-of-kin in this study may carry considerable bitterness if they feel that the Vietnam experience was in any way related to the veteran's death. In fact, the next-of-kin may have filed claims against the government.

We recommend that a trial of at least 25 deceased veterans be conducted during the course of the pilot study, in which an attempt is made to obtain as much information as possible. The success rate and value of the information obtained can be reassessed at that point.

Compensation for time lost from work, and perhaps, additional money might be offered for participation. The Air Force is paying its Ranch Hand participants $100 per day. In addition, the appropriate referral should be provided for any condition requiring medical attention which is detected in the study.

See the response to paragraph 8 of the VFW letter concerning the issues of compensation.

The procedures for notification of subjects concerning medical conditions and referral for medical care are outlined in the study protocol and should be refined during the pilot study. (See also the section on this subject in the AOWG review response.)

Safeguards are necessary so that the initial letter and telephone contacts are handled in a similar manner for all participants. Offering different inducements for participation or making suggestions about exposure status could affect response rates. The recruitment letter needs careful attention. The wording of the sample letter provided with the protocol must be reconsidered. The present form and tone might generate avoidable non-participation.

The suggestion was made that the initial telephone contact might be expanded in order to gather some information. That conversation will be the only source of data for veterans who do not choose to participate. A standard inquiry about demographic and other characteristics should be made at that time if at all possible. The Air Force has developed a minimum data set for this purpose.

> We agree completely that the initial contact and telephone contacts must be handled in a similar manner for all participants. We believe that blinding of the coordinating center and data collection centers as to the cohort membership of the study participants during the data collection phase would obviate this problem. Differential inducements for participation should certainly be avoided. The recruitment letter can be revised by the coordinating center for the pilot study and tested at that time. We would make an additional recommendation which was not made in the original protocol, that serious consideration be given to hiring at least a part-time public relations expert to assist the study in such things as the handling of publicity and inquiries and the design of various contact procedures.
>
> We recommend that the coordinating center obtain the Air Force minimum data set for consideration in the telephone contact.

11. Outcome Assessment

The questionnaire and, to a lesser extent, the medical examinations are mosaics of question segments, mostly drawn from existing instruments, blanketing many areas of possible health effects. The investigators propose to provide as much overlap in data collection as possible with other concurrent studies, particularly investigations of Australian veterans of Vietnam and U.S. Air Force Ranch Hands. This is a strength of the study and should be encouraged. Replication of any findings, whether positive or negative, will strengthen all the investigations.

While OTA appreciates the value of including questions from other studies, there is some unease about the lack of justification for the questions and the seeming lack of focus. There is a need for the investigators to relate questions to the purpose of the study. This exercise is the first step toward developing an overall scheme for interpreting the results. It is a difficult exercise even when dealing with objective information, and it is all the more difficult when dealing with so many largely subjective responses. The interpretive value of various answers and combinations of answers may be, next to the assignment of individuals to the low and high likelihood of exposure groups, the most controversial aspect of the study details. It is, therefore, important that the development of the analytical scheme be carried on in tandem with development of the likelihood of exposure index.

A fundamental point, discussed in our September 8 review of the first draft protocol, is reiterated in the current review: the investigators must specify at least some key outcomes they intend to look for. OTA does recognize, however, that there is merit in looking for as wide a range of outcomes as possible in view of the plethora of complaints alleged to be consequent to Agent Orange exposure. Allowance should be made for some looseness in data collection, for the examination of broad, open-ended hypothesis-seeking questions. The investigators could easily be faulted for failing to look for particular complaints after the study is completed. This does not alter the fact that decisions will have to be made to investigate roughly a small number of key conditions most likely to be associated with Agent Orange, and to exclude those for which little or no support exists. Decisions about key outcomes should be based on previous epidemiologic and animal studies of the components of Agent Orange and perhaps other toxic chemicals, if deemed relevant. The decisions should also take into account some of the more frequently-occurring effects reported in the popular press.

There is bound to be disagreement about the key endpoints chosen initially, but the sooner the initial list is drawn up, the greater the chance for constructive input from reviewers, and the happier everyone is likely to be with the final product. The question of key endpoints must be settled before the questionnaire and medical examinations can be made final.

We understand the seeming lack of focus in the questionnaire. The questionnaire has now been separated into a section dealing with demographic factors, Vietnam experience and the majority of confounders and a separate section, which can be administered at a different time, concerning the medical history. In addition, we have provided in the attached Table II, a list of the groups of questions which deal with specific factors and the reason for their inclusion in the questionnaire. This list may be helpful to the coordinating center in the evaluation of the questionnaire at the time of pilot testing.

As previously noted, the table included as Table I of this addendum gives the endpoints noted in the animal studies, the health effects reported in human studies and our own specification of those outcomes most likely to be seen or which we feel must be included in this study, regardless of their likelihood of occurrence. While we expect considerable debate about this list, it should serve as a starting point for discussion. An additional point about the questionnaire is the wide variety of complaints which have been reported in the popular press concerning the effects of Agent Orange. These are listed in a table in the appendix chapter of the protocol dealing with the popular press. We feel that these topics cannot be completely ignored in the collection of data for the study. Unfortunately the inclusion of such a range of effects also insures a relatively lengthy questionnaire. In the current form, with separation of the medical history section from the rest of the questions, the entire questionnaire should be more palatable because of the administration of segments in shorter time blocks.

We have not included broad open ended questions in the questionnaire for two major reasons: 1) our previous experience has been that diseases not specifically asked for in a questionnaire are not reported by the subjects. This is further confirmed by the established phenomenon that any individual's capacity for recognition exceeds his or her capacity for recall. 2) The difficulty of developing and applying coding schemes for open ended questions would greatly increase the cost of administering the questionnaire and would introduce an additional difficult problem in ensuring standardization.

. Questionnaire

The veteran and spouse questionnaires are made up of questions about health, and non-health characteristics, broadly described as demographic, lifestyle and occupational descriptors. The questionnaires are made up, in large part, of questions and sections drawn from other questionnaires, including the Australian Agent Orange study, the Air Force's Ranch Hand questionnaire and several other general health and lifestyle questionnaires. The questionnaires were generally considered to be the weakest part of the protocol. There was strong feeling that a major overhaul is necessary both in substance and in form before the questionnaires can be used. There was some concern that the interview required to complete the questionnaire would take too long. This was tempered by recognition of the need to acquire hypothesis-seeking information which, of necessity, may be poorly eated. At this time, overcollection is preferable to undercollection. The Panel strongly suggested arranging the sections or questions in the questionnaire and other data collection instruments hierarchically, from the inquiries most vital to those least likely to produce useful information. This hierarchy could guide eventual paring down of the questionnaire if deemed necessary after further field testing. A general suggestion was to encourage the study designers to enlist the help of experts in designing the questionnaires.

The Panel was unclear about the setting in which the questionnaire is to be administered. Some members expressed a preference for administering it, all or part, at some time prior to the medical examinations, and not necessarily at the examination site. If more convenient and numerous locations for the interview could be arranged, e.g. public schools or other public buildings, participation levels t be enchanced. Interviewing in the participant's home was not favored, since

might discourage participation among a subgroup of veterans, including perhaps those who have not shared their Vietnam experiences with their families. This same concern, if it pertains to a large number of veterans, may pose a problem in attaining sufficient participation of wives.

Depending upon the length and content of the questionnaire that eventually is adopted, some thought might be given to "staging" its administration. This ties in with another issue concerning the training and background of interviewers. There might be merit in considering the use of trained medical personnel — nurses or physicians' assistants, for example — to administer the health segment, and other trained interviewers to cover the non-health questions. It might be possible, for instance, to administer the questions on demographics, lifestyle and occupation prior to the time of the medical examinations. This might be particularly advantageous if the questionnaire is long.

Concern was raised that, particularly in the health segment and in the questions dealing with exposures to chemicals both in and out of Vietnam, there was little or no allowance for spontaneity on the part of the participants. Valuable information might be volunteered if the opportunity exists for participants to fill in gaps left by specific questions.

The general health segment suffers from being too broad and sweeping, and the segments concerned with specific key areas do not go into enough depth. This is in large part a consequence of the lack of focus on specific key health outcomes related to Agent Orange. As presented in the questionnaire, the systems of the body

very unevenly covered. The language used for different systems varies from ue and possibly misleading vernacular to highly specific esoteric diagnoses. A entially fruitful area of inquiry, infectious diseases, received no attention at . Information about parasitic diseases, specifically, should be sought.

OTA feels strongly that both diagnoses and symptoms should be sought for all nditions of interest and that certain responses should trigger in-depth probes in y areas. The Panel suggested various models that the investigators might draw on for presenting diagnoses and symptoms, specifically the Kaiser Foundation dical history questionnaire, the Cornell Medical Index and the health history estionnaires of major insurance companies.

he questions relating to neurology are in need of revision. More emphasis uld be placed on functional questions in this area. For example, probing about specific skills that the participant possessed in the past compared with his abilities now could uncover changes in neurologic status. The questions should be restated and terms added to be more inclusive in describing sensations. These were not well-described.

The approach to malformations in offspring was considered deficient. The spouse questionnaire is not specific enough about exposures of the mother during each pregnancy, and no attempt is indicated to interview or obtain records of previous partners or spouses. Questions about smoking and drinking should be asked specific to each pregnancy. Questions about medications known to be teratogenic should be asked directly. No information about pregnancies resulting in perinatal s, often occurring in babies with birth defects, is gathered. This should be rrected. If a birth defect is reported by either the participant or spouse, an attempt should be made to verify the diagnosis via medical records.

See above comments.

The protocol recommends administering the questionnaire at the examination center during the course of the examination procedures. We feel that this procedure is mandatory. The administration of the questionnaire prior to the scheduled examination would probably increase the dropout rate during the interval between the interview and the conduct of the physical exam. We are generally uneasy about the use of trained medical personnel for administration of the medical history section because of the general finding that medically trained personnel are poor interviewers and have difficulty following precisely a standard protocol. Use of properly trained (in questionnaire administration) nurses or physicians assistants would have the advantage of better understanding of the medical conditions included. The danger is that these medically knowledgeable interviewers would make judgements about the "correctness" of the veteran's responses and introduce a potentially serious bias. We do, however, recommend that the results of the medical history section be provided to the examining physician at the time of physical examination.

The reviewers were concerned about lack of depth in many areas. Much of the lack of depth is deliberate since we felt that the veterans would generally have difficulty in answering specific technical questions. (Note that we have removed all questions about specific diagnostic tests from the revised questionnaire.) However, in all cases the veterans will be asked for the name and address of the diagnosing or treating physician or hospital. The necessary technical detail can then be obtained from this medical source.

We do not agree that information about tropical infections and parasitic diseases should be included in the questionnaire. Although it is likely that many veterans may have acquired parasites in Vietnam we are not aware of any basis that this is associated with exposure to Agent Orange. We feel, therefore, that inclusion of questions on these diseases would add complexity and length to an already long, complex questionnaire without adding commensurate relevant information.

Some of the scales from the Rand Health Insurance Study for physical and mental health status might be considered as additional data collection procedures because they have been well tested, and normative data will be available on a large population by the time this study is completed. We know, however, of no simple and useful method for assessing changes in functional level. We have added several questions from the NCHS questionnaires.

The administration of the spouse questionnaire to previous partners or spouses is strongly recommended in the protocol and reemphasized here. The verification of birth defects by use of medical records should certainly be included as should verification of any other reported condition.

b. Laboratory Tests

The laboratory tests included in the protocol were heavily criticized as inappropriate and generally not leading to any conclusions about exposure to toxic substances. OTA recognizes the difficulty in choosing appropriate laboratory tests, however, since none is specifically diagnostic for the effects of Agent Orange or its constituents. The point was stressed that the participants will be relatively young and healthy, and for the most part we should be looking for early markers of disease and not frank undiagnosed cases of most conditions. The selection of the study participants on whom the tests in Table 3 will be performed is not discussed. Just as for questionnaire and other medical examination items, the justification for laboratory tests should be included, and the conditions that can be detected by them, either alone or in conjunction with information from the questionnaire and physical examination, should be specified. In light of the recent publicity about melioidosis, some serological testing for evidence of exposure to infectious diseases might be considered. This is not advocated, however, if the tests available are not well standardized or accepted as meaningful.

An example of the potential difficulty in interpreting laboratory tests was brought up by one panel member. Laboratory values obtained from an individual might have no relevance whatsoever to an individual's exposure status in 1969. This is important because aberrations in levels of many enzymes, hormones, etc., are often reflective of acute rather than chronic conditions. For example, an elevated urine white blood cell count could be the result of a lower urinary tract infection occurring one week before the sample was drawn and not have any relevance to an

ividual's Vietnam experience. Therefore, one aspect of the rationale for interpretation is to put into proper perspective the meaning of aberrant levels detected in laboratory tests.

Another aspect of interpreting these types of laboratory tests involves the reported result itself. Most laboratory tests have published reference ranges or so-called normal ranges, which are considered to be important clinical tools. There is, however, some controversy regarding their utility for epidemiologic study. What does it mean if the study group has more individuals with values outside a given reference range than the control group? Does it have biological significance or is it a consequence of the reference range's being too narrow for this group? In some cases, actual values can be reported (e.g., hematocrit, percent lymphocytes) and analyzed, circumventing the problem of the reference range. However, with variables ch as urine protein, the values are usually reported as being within or outside the reference range and interpretation is difficult. Perhaps such variables should be considered only with respect to an individual's clinical presentation and not considered as epidemiologic outcomes.

Another related problem involves the possible finding of a significant difference between study and control groups which cannot be biologically explained. For example, what does it mean if the study group has significantly elevated red blood cell counts, a condition usually not considered detrimental? Will this be reported as a cause for concern?

There are, then, at least four areas pertaining to the analysis and interpretation of the laboratory aspects of the study which require guidelines for terpretation: the meaning of aberrant levels detected in laboratory tests, the significance and/or usefulness of reference ranges, clinical versus biologic interpretation of data, and a definition of areas of concern.

The laboratory tests recommended for this examination were developed with our internal medicine consultant in conjunction with the development of the physical exam and were designed to be complementary to that physical examination. It was further developed to ensure as much comparability as possible with the Air Force study. Further consideration of appropriate tests can be given by the Oversight Committee and coordinating center during development of the pilot study.

The selection of study participants for administration of the tests described in Table 3 are specified for each test in the table itself.

The interpretation of laboratory results can be made in two distinct ways, 1) clinical interpretation and 2) population interpretation. The clinical interpretation, in which the laboratory value is related to other examination information and a determination is made of clinical meaning for each individual, should be made by the examining physicians in conjunction with the coordinating center as outlined in the protocol. Appropriate notification of individuals and referral for appropriate care should be made as necessary. Normal ranges are useful in such clinical interpretations. For the population interpretation the distributions of laboratory values are determined for the comparison study groups. Since, as noted in the review, the participants will for the most part be young, healthy men we feel that the laboratory tests should be examined with the view of detecting biologic alterations which may have future implications for the health of individuals rather than relying on strictly clinical abnormalities. By the use of distributions of the laboratory values, the problem of normal ranges will not arise.

A cutoff value should be established for each laboratory procedure. This cutoff should be determined by the coordinating center in consultation with the appropriate laboratories and other expert consultants. To reduce laboratory errors, any value found outside the specified cutoff points should be retested on the same or, if possible, a new specimen.

The reviewers were concerned about what criteria would be used to determine which findings were cause for concern. We feel that any consistent differences in which the exposed group are "worse" than the unexposed and which cannot be explained in any other way should be considered cause for concern.

c. Physical Examination

The physical examination included in the protocol is adapted from that to be used in the Australian study, and it is a good starting point for the VA study. Panel members made a number of specific suggestions, included in this review in Attachment B. Some general points also were brought out. The physical exam should be "Americanized," though comparability with the Australian study should be preserved as much as possible. Systems for scoring items and examination techniques should be based on current American practice. Training for the medical personnel carrying out examinations should not be devoted to learning new scoring systems. Some of the items in the examination are too general, where specific conditions should be noted.

See the comments under the Agent Orange Working Group review.

d. Neurologic Examination, Psychologic Assessment and Neuropsychologic Assessment

The group of test instruments proposed to assess neurologic, psychologic and neuropsychologic status was generally considered strong. A number of improvements were suggested, the more specific of which are included in Attachment B.

The neurologic examination requires modification to focus more clearly on peripheral neuropathies. At present, some of the critical muscles are missed and appropriate examinations should be added. It was suggested that an audiogram be added as well. There are some questions requiring greater quantification and others requiring changes in explanations of the grading system. The question on mental status should be replaced with some objective measure, as the subjective remarks of examiner would be difficult to interpret.

Regarding the psychologic assessment, the MMPI and SCL-90 have their strength in measuring depression and anxiety. An effect, if present, should be evident with these tests. SADS-RDC is not considered the "state-of-the-art" in many diagnostic categories, though for schizophrenia it is probably the best. NIMH is performing a cross-sectional screen on 15,000 individuals using a new scale called DIS, Supposedly it can differentiate schizophrenia, depression, phobias, obsessions, drug abuse, alcoholism and anti-social behavior with the last three items being the strongest. This obviously would be important in the veteran population. Since the scale for schizophrenia was weaker in DIS, the possibility of creating a hybrid between SADS and DIS might be considered. The DIS can be administered by a lay person and takes approximately 90 minutes.

The neuropsychologic test battery is well chosen for measuring effects of any brain damage if present. The sensitivity will be increased if results can be compared to test results from the veteran's induction examination. One Panel member

a cautionary note about factors that must be considered in interpreting test results. In addition to age and education, native language is important. Verbal fluency in the controlled word associations and vocabulary are two examples that might be significantly altered by a native language other than English. The questionnaire at present does not include an inquiry about native language. Finally, it appears that these tests will take longer to administer than has been estimated in this protocol.

The Diagnostic Interview Schedule (DIS) is a structured interview with precoded, close-ended symptom items which yields DSM-III diagnoses; it is computer scorable and can also be used to generate Research Diagnostic Criteria (RDC) classifications, a precursor of DSM-III. The DIS is administered by lay interviewers whereas the Schedule for Affective Disorders and Schizophrenia (SADS) is administered by clinical interviewers. Therefore, the DIS is less expensive and more readily administered than the SADS. The strength of the SADS, however, lies in its reliance on the clinical expertise of the interviewer who makes the RDC ratings on the basis of the structured interview guide. The DIS is currently receiving extensive, full-scale field testing as part of the Epidemiological Catchment Area projects sponsored by NIMH, as well as being validated on clinical populations. At present the instrument has not been totally standardized, as there is a lack of consensus on the criteria for generating current diagnoses. The DIS could constitute an acceptable alternative to the SADS-RDC although the field testing and validation may not be completed in advance of this study. Since these two instruments differ so widely in method of data collection, creating a hybrid is probably not feasible.

We certainly agree that a question concerning native language should be included in the questionnaire and the question has been added. Those veterans identified as non-native English speaking should be analyzed as a separate group when comparing results of the neuropsychologic scales which involve language fluency. The estimated administration time for the neuropsychologic tests was developed by an experienced neuropsychologist. The estimates can be refined on the basis of experience from the pilot study.

Release of Medical Records to the Study

The protocol proposes that the study contractors request release of rticipants' medical records for use in the study. In general, there was a feeling hat such records would have limited value. Concern was expressed that Agent Orange s such an emotional subject that a participant who presented himself to his family hysician claiming ill effects from exposure might receive examinations and iagnoses different from a person who did not think he had been exposed to the erbicide. Additionally, it would be difficult to determine possible biases introduced by use of some medical records but not others. It was suggested that the time to make a final decision on this would be at the completion of the pilot test, when the yield from such an effort could be assessed.

Army induction examination records might be useful in establishing baseline values for some measurements. Those records suffer from many shortcomings, but they are collected in a routine manner, and they might be of value in the general health and psychologic areas. The usefulness of those records should be assessed.

If the effort is made to obtain medical records from participants, provision should be made for requesting release of children's medical records, as well. Such records would be of value in determining whether a birth defect might have resulted from exposure to toxic substances or from another cause. Likewise, medical records from ex-partners might be useful in the case of children borne by women other than the current spouse or partner.

We agree with these comments.

12. Data Analysis and Sample Size

The discussions of data analysis and sample size were well presented and thorough treatments, at least for certain aspects. However, there is no discussion of how confounding variables are to be handled in the analysis. This subject must be further developed.

The data analysis plan seem clearcut and logical. The notion of obtaining a handle on reporting bias is laudable. However, it is not clear just how a comparison of "those reporting exposure but not verified to have had exposure with those verified to have had exposure but not reporting exposure" (page 101) will provide the requisite information. Further, if this comparison shows some meaningful differences, what then will the investigators do in analyzing their results?

The remaining statistical analyses are generally straightforward, and and well presented, if not in full detail. Since there presently exists a fair degree of vagueness regarding the particular health outcomes implicated, the investigators cannot be faulted for their lack of detail regarding statistical analyses.

The sample size determination, made with reference to the limited information now available, is clear and pertinent to the proposed study. The requisite sample size, as the investigators indicate, can be more firmly determined following completion of the pilot study.

The choice of 0.01 and 0.05 for type I and type II error probabilities, respectively, is unusually severe. The investigators should consider relaxing the type I error at least, perhaps to the more customary 0.05 level. Adhering to a level of 0.01 seems to move this research study unnecessarily into a decisionmaking arena. Strength of association should be expressed by point estimates along with pertinent confidence intervals.

The choice of a 30% cutoff for combined nontraceability and refusal to participate raised concerns that such strictness might make the study impossible. An overall participation rate of 70%, which the investigators require, would be considered quite good for many studies but, according to the Panel, would likely be unachievable in this case. A somewhat lower participation rate was thought to be more realistic. Obtaining minimal information on essentially every participant at the time of the initial contact would reduce the impact of non-participation. On the other hand, adhering to the criterion of a difference in participation rates of no more than 15% between the high and low likelihood of exposure groups is considered appropriate.

22) The question of confounding variables is addressed in section D and E in the protocol section on data analysis. There are a number of ways in which confounding variables can be handled, or at least accounted for in analysis. For instance, various adjustment procedures, stratification and covariance analysis can be utilized. Logistic regression and log linear analysis, can also be employed.

The question concerning reported exposure versus verified exposure can be answered utilizing the fourfold table below of reported versus verified exposure - or sensitivity or specificity of reported exposure as a measure of verified exposure. (The letters represent the veterans in each cell.)

		Verified exposure: yes	Verified exposure: no	
Reported Exposure	yes	a	b	a+b
	no	c	d	c+d
		a+c	b+d	

In the usual fashion c represents false negatives and b false positives.

If the exposure was indeed damaging, then one would expect those with verified exposure, reported or not, to have "more" outcomes than those without exposure (i.e., disease rates among a+c greater than among b+d); the relative risk, given exposure would be greater.

One would also expect that the rates in a and c would be similar to each other, as would those in b and d. Therefore, one might expect the false negatives, c, to be meaningfully different from the false positives, b. In fact, such a difference might vindicate the verification procedures for exposure.

If the exposure was not damaging, then one would expect no difference between the exposed (a+c) and unexposed (b+d), hence no difference between the false negatives and false positives.

If, however, there is an impact associated with belief in exposure in the absence of actual impact, then one might expect that the relative risk given reported exposure would be greater (rate among a+b > among c+d). In this case the false positives might be expected to be substantially worse off than the false negatives. This type of difference might imply a differential reporting or recollection in the presence of a belief in exposure. Such a finding would call for a reexamination of the exposure verification procedures to assure that there is no error, and might call for reinterview of veterans to assure that the records do reflect their actual locations and experience.

If there is some impact associated with verified exposure and some impact associated with belief in exposure, then one would expect that the true positives (a) , who both believed themselves to be exposed and were exposed would have the highest rates (worst outcomes). The false negatives (c) and the false positives (b) would both have lower rates, the direction of their difference from each other depending on the risk associated with exposure and with belief in exposure. Those neither exposed nor reporting exposure (d) would have the most favorable outcomes.

In sum, a meaningful difference between false negatives and false positives has great importance as a finding in the study. The direction of the difference combined with comparisons with true positives and negatives will yield important evidence of relationships of exposure, belief and outcomes.

The reviewers suggest considering relaxing the type I error to a 0.05 level. We chose the level of 0.01 because of the seriousness of making an α error and for purposes of sample size computation. Once the study has been conducted the results can be reported with the actual significance levels and the interpretation of those levels can be made by to the reader.

The reviewers also feel that our criterion of an overall participation rate of 70% is likely to be unachieveable for this study. Our experience in a somewhat similar study tracing men from as long as 25 years ago and the experience reported by Eckland (Bruce K. Eckland, Retrieving Mobile Cases in Longitudinal Surveys, Public Opinion Quarterly, p. 51-64, Spring 1968), suggest that, with appropriate diligence and the wide variety of tracing resources available, more than 85% of the cohorts should be located. We feel that reduction of the overall location and participation rate to below 70% would leave the study results open to serious question.

Listed below are the specific comments from Attachment B. Our response or action concerning each comment is also given.

I. Comments on Protocol Text

page 11 "Time-bomb" idea - imponderable but not necessarily improbable.

We still feel this proposed mechanism is improbable.

page 15 para 2, l.4 "known very heavy exposure to Agent Orange." Even in Ranch Hand, exposure is presumed rather than known.

We agree, although the probability appears to be much higher.

page 20 para 1, l.2 "presumed highly . . . exposed." Even the higher exposure group will not necessarily be "highly" exposed. "Higher exposure group" might be more accurate.

"Higher exposure group" might be more accurate but every attempt should be made to establish a cohort with as high a likely exposure as possible.

page 25 Step 5, l.5 insert "likely," to read "number of likely exposures he encountered."

We agree.

nments on Questionnaires

page 10 Question concerning agricultural exposures needs more attention. An agricultural specialist might be consulted to develop a set of questions which would fully probe possible exposures to agricultural chemicals. Lists of all generic and trade names of chemicals should be supplied. Hygiene habits after exposure to such chemicals should be probed as well.

We felt that additional detail would be too cumbersome and unlikely to yield good data. We have specified the general classes of chemicals of interest.

page 89, (e & f) Why are epilepsy, and convulsions or seizures separated when they are identical? How will it be rated if an individual answers yes to both versus just one?

Epilepsy, and convulsions or seizures are separated because many people will not respond positively to one or the other, particularly epilepsy. These can be combined in analysis as if they were one question.

page 89, (h) Head injury is often a problem of the past. It helps to determine severity by asking if loss of consciousness occurred, since such episodes are often treated in emergency rooms.

Done

page 95 Double vision and blindness in one eye are too limited; should include dimming of vision in both eyes? or one eye?

Revised

A question should be included regarding cramping in the calves since this is a common presentation in early peripheral neuropathy.

Done

Previous medication history is not covered. It is not enough to know what medications a person is currently taking.

We have included a question about past medication taken regularly for 3 months or longer

Sexual preference is not queried. It is important to ask about this since homosexuals disease patterns appear to be different from that of heterosexuals.

We do not feel that the responses would be accurate enough to be worth asking.

A question about cocaine use should be added.

Done

More questions dealing with "social health" should be included, covering marital history, migration, involvement with the criminal justice system, credit problems. These items could be verified through legal records.

Several questions have been added. Migration can be estimated from the residence history. We felt that many such questions would be considered offensive by the veterans. Note that an assessment of the veteran's financial status could be independently obtained by conducting routine credit checks. The coordinating center could establish an account with appropriate credit agencies for this purpose.

The reproductive section of the spouse questionnaire inquires about labor and delivery problems only for live births. This should be expanded to include all births.

Section revised

The spouse questionnaire should include questions specifically about use of anti-coagulants and spermicides, both of which may be teratogenic.

Done

I. Comments on Physical Examination

These comments were reviewed by a professor of Internal Medicine at UCLA and the necessary changes made according to his guidelines.

Urinalysis does not use American dip-stick categories of 1+ to 4+. Also, room to identify the type of cast is needed.

The urinalysis is part of the laboratory procedures and has been deleted here.

A.7.d. "Nasal Mucosa Normal" is too general. There are specific abnormalities to be noted.

See changes on form.

B.2. a&b. Not sure that one can safely differentiate acute from chronic otitis externa on a single examination. Need more objective findings.

See changes on form.

C.2. c. Need a basic fundoscopic examination.

Fundoscopic exam addeds as C5.

D.1. Need an objective determination of lymphadenopathy.

There is already a place for description of the lymphadenopathy. We are not sure what else was desired.

D.2. Room is needed for description of abnormalities.

Added.

E.4. Gynaecomastia - unilateral or bilateral?

Added.

E.5. Clubbing needs to be added, here or elsewhere.

Added under L4.

E.6. Need respiratory rate.

Added.

E.9. This is an English-based classification, probably useful for this purpose. If used, we need anterior as well as posterior.

Our consultant feels that there is considerable confusion now about the best way tc describe respiratory sounds. He feels the system should be left as is. We have added a check for anterior/posterior location.

F.4. Need to describe how high jugular venous pressure is, not yes/no.

Added.

F.8. Need to distinguish ejection click from late systolic click. Also, splitting of S_1 and S_2 needs to be noted.

Added.

.9. Americans rate murmur on a scale of 1-6. Also needed is an opportunity to assess the murmur.

We agree that the scale could be changed but do not feel that it would add much.

F.10 a.b. These questions are very subjective. Should be asked only after questions of foot temperature, presence of ulcers or other skin changes. Pulses should precede any assessment of whether ischemia is present.

See changes on form. Patients can have small vessel disease with ischemia in the presence of normal pulses.

G. Probably need a question on whether guarding or tenderness of the abdomen. Also whether a pulsatile, enlarged aorta.

Questions on guarding/tenderness added. Category G.7. allows for description of other abdominal masses.

G.4. Need objective definition of hepatomegaly.

The objective measurement of liver span was in the form already.

G.5. Need objective definition of splenomegaly.

See changes on form.

J.a. Need to ask about prostatic nodules, rectal masses, hemorrhoids or other lesions.

See changes on form.

K. Need room to describe positive findings.

We do not see a need for any more description of the back.

K.8.a. Pain where?

See changes on form.

L.3. Should include specific test for carpal tunnel syndrome.

See changes on form.

M. Need room to describe positive findings.

A great many abnormalities are specifically questioned and room is provided under M12 for description of any more abnormalities.

M. 13. Need objective definition of obesity.

Since even bariatricians who deal with obesity have trouble defining exactly how obesity should be described we do not know how this should be further addressed. Note, however, that current height and weight are measured.

M.14. What is the purpose of this question?

This question was included to help interpret an abnormal glucose tolerance test which could be on the basis of lack of propoer carbohydrate loading.

Possible additions to physical examination.

-presence of xanthoma, xanthelasma
-presence of pallor.
-body habitus (e.g. Marfanoid)
-other endocrine-related conditions — feminization, body hair, striae, dorsal hump - fat distribution, Achilles reflex relaxation phase.

Xanthoma, xanthelasma, pallor and striae added under skin. Body habitus has been added as M.15. Deep tendon reflexes are examined in the neurologic exam. Feminization has been covered by questions on gynecomastia.

V. Comments on Laboratory tests.

Tables 2 and 3 in the protocol were misplaced. There appears to have been some confusion as a result of this.

Semen analysis must be specifically defined since there are several semen parameters which may have biological relevance.

Defined in Table 2

Testosterone has not been shown to be a definitive predictor of testicular pathology or reproductive malfunction - most studies, however, have not distinguished between free or weakly bound testosterone (which is the biologically active steroid) and testosterone bound to sex-hormone binding globulin (inactive). The investigators should consider examining both total testosterone and free/weakly bound; studies which have considered the relative predictive value of sex hormones for testicular pathology have indicated that follicle-stimulating hormone has perhaps the most predictive value--albeit weak. The investigators should consider (1) the feasibility of conducting any sex hormone analyses at all since past studies do not suggest they are of great value and (2) if hormone analyses are included, follicle stimulating hormone and luteinizing hormone should be added since they also play important roles in the interactive relationships among the hypothalamus, anterior pituitary and the testis.

See Table 2. We would agree with adding free and total testosterone

A resting and step-electrocardiogram is proposed. It is hard to understand what would be identified from the electrocardiogram in this age group that could possibly be related to agent orange, nor the value of a simple exercise using a stool done in many centers in the United States.

3. We agree that a step-stool ECG would probably not be of much value. A treadmill ECG would be preferable. A thallium treadmill ECG would be still better but more costly. The relative merits of these tests can be further considered in the pilot test. The ECG is, like many other tests, necessary for a thorough evaluation of possible Agent Orange effects.

A renal screen is proposed, based on doing a simple urine analysis. It is unlikely that this would yield any useful information. Perhaps a dip-stick for protein would show something but a tremendous number of men in this age group will have protein in their urine early in the morning.

> See Table 2. The renal screen includes a BUN and if that is abnormal a creatinine.

A series of measures are proposed for liver function, which also are essentially crude and unlikely to yield any useful information. Urinary porphyrins might be of interest because of the possibility of porphyria related to agent orange, but it would obviously make much more sense to look for patients with porphyria and determine whether they had been exposed to agent orange.

> Elevated serum hepatic enzymes are a major postulated outcome and must be included. Urinary porphyrins were included (see Table 2).

The blood counts, again, offer no hope of any useful information.

> We disagree. The comparison of population distributions could be of value and should be done.

Spirometry is proposed. It is unlikely that routine FEV, and FVC, considering the tremendous effects of cigarette smoking, and other environmental factors, would be of any use.

> We disagree. Smoking histories and environmental exposures are collected in the questionnaire and can be incorporated into the analysis.

Comments on Neurologic Examination

The neurologic examination form has been revised.

Under tone, how does one include subtypes, such items as cogwheeling, etc.?

See revised form

Strength - must quantify; should use standard 0-5 scale. Peripheral neuropathies involve most distal muscles; therefore, must examine intrinsics of hand. Distal wrist extensors is fairly specific for lead neuropathy. In foot, extensor digitorum brevis (forms toes) is distal muscle usually affected first in peripheral neuropathy.

See revised form

Abnormal Movements - What does the grading system (1-4+) mean? It should be tabulated in the same fashion as the reflex responses.

See revised form

Mental Status - How can this be left open ended? A standardized mini-mental is one possibility. It would be very difficult to grade an examiner's subjective remarks.

Even when dealing with trained neurologists, each does the exam differently with grading systems dependent on his place of training.

See revised form

On page 55, under nerve conduction velocity, the sural is the only sensory measurement listed. Considering that even in toxic neuropathies which are predominantly motor, the sensory nerves may demonstrate electrical abnormalities first, both the ulnar and peroneal sensory latency and amplitude should be included. Amplitude is an important measurement since it reflects the number of axons involved in the action potential. Toxic neuropathies are usually axonal and therefore may demonstrate disease with a decreased amplitude before prolongation of the distal latency. Also it should be noted that the sural nerve may be congenitally absent.

We agree that the ulnar and peroneal sensory latencies and amplitudes should be included. However, after the pilot study the potential usefulness of all of the nerve conduction tests should be re-evaluated.

If electrodiagnostic abnormalities are found or clinical evidence of a neuropathy is present, conduction measurements should be extended to the median and posterior tibial. This will help differentiate entrapment neuropathies from polyneuropathies.

We agree.

TABLE I

A. Effects Reported in Animals - subacute and chronic toxicity

chloracne

porphyria cutanea tarda

hepatic necrosis

liver insufficiency

decreased renal function

↓ prolactin, FSH, progesterone, estradiol

↑ abortions, stillbirths

thymic atrophy

immunosuppression - especially ↓T-cell function at higher doses
↓humoral immunity

↓ resistance to bacterial infections

thrombocytopenia

leukopenia

↓ body weight gain

lymphopenia

anemia

hemorrhage

teratogenicity

activation or suppression of liver enzyme systems

mutagenicity

carcinogenicity

B. Effects Reported in Humans

chloracne

hirsutism/hyperpigmentation

loss of libido

porphyria cutanea tarda

↓ hepatic function (interaction with alcohol)

↑ serum hepatic enzymes

↑ triglycerides, cholesterol, phospholipids

altered total/HDL cholesterol ratio

abnromal GTT

hypertension

MI's

bronchitis

↑ susceptibility to infections

TABLE I (cond)

B. Effects Reported in Humans (continued)

polyneuropathies
lower extremity weakness
sensory impairments (sight, hearing, smell, taste)
CNS disturbances
↓ nerve conduction velocities
birth defects
miscarriages
psychiatric effects (range)
soft tissue sarcomas
liver cancer
stomach cancer
malignant lymphomas
testicular cancer
symptoms particularly of: respiratory system
GI
CNS
skin and eye

C. Most Likely List (from animal and human literature)

chloracne
porphyria cutanea tarda
hepatic insufficiency or ↑serum enzymes
hirsutism/hyperpigmentation
↑ susceptibility to infection
cancers
peripheral neuropathy
activation or suppression of renal enzyme systems
reproductive effects (stillbirths, abortions, infertility, teratogenicity)
psychiatric disorders
altered fat metabolism (↑cholesterol, triglycerides, phospholipids)
asthenia

TABLE II

AGENT ORANGE QUESTIONNAIRE TOPICS

Questions Numbers	Topic/Reason for Inclusion
Veterans Interview	
1	identifier
2-7	demographic
8	identifier and reliability and validity check
9	identifier
10	residence - confounder and measure of mobility
11-13	childhood family SES, cohort comparability check
14-17	occupational and exposure history - confounders
19-20	functional questions and Alamedo County Population Laboratory Health Habits Scale
21-22	social functioning
24-32	military history/Vietnam exposures
33-34	SES status
Medical History Questionnaire	
1-3	family health history
4-6	military health history
7	other injuries - confounder
8	surgery history
9	hospitalizations health status indicators
10-11	medications
12	malaria prophylaxis - confounder
13	infections - outcome
15-36	cigarette/tobacco - confounder
37-38	alcohol consumption - confounder
39-45	drug use - confounder
46-48	weight change - disease indicator
49-54	skin - major outcome
55-56	ear/eye diseases
57	headaches
58-60	heart/circulation
61-63	respiratory disease
64-78	MRC/ NHLBI chronic obstructive lung disease questionnaire
79	Diabetes Mellitus - confounder

TABLE II (cond) AGENT ORANGE QUESTIONNAIRE TOPICS (cond)

Question Numbers	Topic/Reason for Inclusion
Medical History Questionnaire (cond)	
80	thyroid
81	gout
82-83	GI conditions
84	liver disease - major outcome
85-88	kidney
89	cancer - major outcome
90	allergies
91-92	autoimmune diseases - major outcome
93	nervous system - mix of major outcomes and confounders
94-100	nervous system symptoms - major outcome
101-112	reproductive system - major outcome plus confounders
113	hematologic effects
114	gland enlargement
115	blood transfusions - confounder
116-118	bones/joints
119	endocrine
120	emotional - major outcome
Spouse Questionnaire	
1	identifier
2-7	demographic
8	identifier
9	residence history - confounder
10-12	childhood SES - confounder
13-16	occupational/exposure history - confounder
17-23	drug use - confounder
24-26	height/weight - endocrine
27	chronic disease - confounder
28-31	confounders
32-36	health status - confounders
37	teratogenic medications
38-43	fertility
44-49	detailed reproductive outcome and confounders
50	Vietnam exposure
51-56	assessment of veteran's functioning in family - outcome
57-78	SES measures

Science Panel
June 25, 1982

Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

JOHN H. GIBBONS
DIRECTOR

June 11, 1982

Honorable Robert P. Nimmo
Administrator
Veterans Administration
810 Vermont Avenue, N.W.
Washington, D.C. 20420

Dear Mr. Nimmo:

In my letter to you of March 18, 1982, I approved the protocol for the Veterans Administration (VA) study of possible long term health effects resulting from exposure to Agent Orange in Vietnam, subject to the resolution of certain points of concern. Specific questions and criticisms of the protocol that I reported to you in the letter and in the Office of Technology Assessment (OTA) review were forwarded to the protocol designers at the University of California at Los Angeles (UCLA) by the VA. The UCLA response to the OTA comments was included in their mailing to VA dated April 28, 1982. That response addresses OTA's concerns, and, except for two specific areas, the protocol is basically sound for use in a pilot study. The two exceptions are in the sections dealing with the neurologic and psychologic assessments. A copy of the neurologic examination, noting some specific problems, is being sent to the VA.

The revised neurologic examination is an improvement over the previous version, and we now note no major omissions in coverage. The lack of any explanatory material accompanying the examination form, however, makes it impossible to know exactly what is required of the examiner. Speculation about neurologic effects of Agent Orange is rife, making this portion of the protocol particularly important. Additional attention is required to produce a standardized examination, tailored to this study, with as little ambiguity as possible remaining in the design, layout and language. *

On the second point, the psychologic examination, we would like to offer some information that may not have been available to the UCLA contractors. In the OTA review of March 18, 1982, we suggested that a new instrument, the Diagnostic Interview Schedule (DIS), be considered as a replacement for the examination specified in the protocol, the Schedule for Affective Disorders and Schizophrenia (SADS). DIS may have a number of advantages over SADS, both in the conditions it identifies, and in requiring only a lay interviewer to administer it, as opposed to the requirement of a psychiatrist to administer SADS. In the UCLA response, concern was expessed that DIS may not be validated in time to be of use in this study. According *

to recent information, data collection for two of the three major validation studies (those carried out by Johns Hopkins and Yale) is complete, and some preliminary analysis has been completed in the case of the former study. Full analysis from at least the Johns Hopkins study is expected in the fall of this year. We therefore feel that the DIS should not be rejected at this time, and that it be given further consideration as validation data become available.

It appears that the actual epidemiologic study carried out under VA's aegis may differ in one significant aspect from the plan developed by UCLA. The Agent Orange Working Group (AOWG) strongly recommended in its review of the UCLA protocol that the study be expanded to include a third cohort of veterans. UCLA calls for two cohorts: (1) a group of Vietnam veterans who were likely to have been exposed to Agent Orange and (2) a group of Vietnam veterans who were likely not to have been exposed. The AOWG proposes adding an additional cohort: (3) a group of Vietnam-era veterans who did not serve in Vietnam.

The third cohort would broaden the study and allow examination of the "Vietnam experience" as a possible influence on health. The argument for inclusion of the third cohort is powerfully bolstered by consideration of economy: one study to inquire about both Agent Orange and the Vietnam experience, and of timeliness: the possibility of answering both questions at the same time.

The UCLA response to the AOWG suggestion does not favor the expansion. In the OTA review, we expressed misgivings about including the third cohort as simply an add-on to the two-cohort "Agent Orange only" study designed by UCLA. We are not, in principle, opposed to expanding the study. Should the third cohort be added, our concerns about maintaining the integrity of the study can be addressed by (1) discussion of the health outcomes and health indicators to be examined in the expanded study, and why those outcomes should be associated with health sequelae of war as well as exposure to a toxic substance, Agent Orange; and (2) justification for the inclusion of veterans selected for the third cohort. It is important that the third group be as nearly like the other two as possible. UCLA has suggested that, should the third cohort be assembled, it be composed of veterans who were scheduled to go to Vietnam, but who did not actually go. Such a group appears to offer a good opportunity to minimize differences, predating military service, between the third cohort and the other two cohorts. In whatever manner the third cohort is chosen, if a third cohort is included, appropriate tests of comparability with the other two cohorts should be designed and carried out. If it appears impossible to achieve a reasonable degree of comparability, the suggestion of adding a third cohort should be reconsidered.

Because UCLA has satisfied its contractual obligation of developing the protocol for the study of Agent Orange, the details of adding the third cohort would fall to another party. Careful consideration of endpoints and of possible selection bias is a necessary part of adding a third cohort. In keeping with OTA's Congressionally-mandated responsibility to review the protocol, I shall want to see the details and justification about endpoints and selection bias, in the form of a unified protocol for the entire study.

With or without the addition of a third cohort, we are nearing the end of the design phase of this complicated venture. Should you or your staff have any questions, please call Dr. Michael Gough, project director of the OTA review, or Ms. Hellen Gelband at 226-2070.

Sincerely,

John H. Gibbons

Enclosure: Comments on Agent Orange
Neurological Examination

COMMENTS ON AGENT ORANGE NEUROLOGICAL EXAMINATION

General

The examination lacks any explanatory material concerning exactly what is required of the neurologist administering the examination. The examination form is not self-explanatory. Unless directions are explicit, each examiner will rely on his or her background and training to fill in the gaps. Neurological training is far from uniform, and it is dangerous to assume that, for instance, all neurologists will interpret a "standard 0-5 scale" identically.

Basically, all that is needed to make the proposed examination a sound one is some tightening up on details (suggested changes are included on the enclosed copy), a clean-up of the form itself, and a reconsideration of the mental status component.

HEAD AND NECK - Normal to Palpations/Inspection ☐Y ☐N Specify Scar ☐
Asymmetry ☐ Depression ☐
Carotid Bruit ☐No ☐R ☐L
Neck Range of Motion ☐ Normal or Decreased to ☐ Left ☐ Right ·
☐ Forward ☐ Backward

TRUNK

MOTOR SYSTEM - Handedness Right ☐ Left ☐

Gait ☐ Normal or ☐ Broad Based ☐ Ataxic ☐Small Stepped ☐Other-Specify
Associated Movements ☐Arm Swing ☐Normal or Abnormal ☐R ☐L
Muscle Status (strength, tone, volume, tenderness, fibrillations)
Bulk ☐ Normal ☐Abnormal
Tone Upper Extremities ☐Normal or ☐Increased ☐Decreased ☐Other - specify
☐Right ☐Left
Lower Extremities ☐Normal or ☐Increased ☐Decreased ☐ Other - specify
☐Right ☐Left
Strength (quantify using standard 0-5 scale) — Need specific instructions (like those supplied for "Reflexes"

Proximal	Right	Left
Deltoids	____	____
Hip flexors	____	____
Distal		
Wrist extensors	____	____
Interossei	____	____
Ankle dorsiflexors	____	____
Toe dorsiflexors	____	____

Abnormal Movements
Fasciculations ☐ no ☐ yes - specify
Tremor ☐ no ☐ yes - specify
Others (tics, chorea, etc.) ☐ no ☐ yes - specify

Coordination (a) Equilibratory - Eyes Open — What does this mean? How is it to be assessed
Eyes Closed - Romberg ☐Positive (Abnormal) ☐Negative (Normal)
What does this Right Foot — Left Foot
far to? one-footed mberg?
(b) Nonequilibratory (F to N; F to F; H to K) Finger-to-nose-to-finger
☐Normal ☐Abnormal ☐Right ☐Left ☐Both — no place
Heel-Knee-Shin ☐Normal ☐Abnormal ☐Right ☐Left ☐Both to score
(c) Successions Movements (including check, rebound, posture-holding) — this
If indicated, check ☐Normal ☐Abnormal ☐R ☐R
is explanation — Rapidly alternative movements ☐Normal ☐Abnormal ☐R ☐L ☐Both
Skilled Acts (a) Praxis - How is this to be assessed?
(b) Handwriting. If indicated, ☐Normal ☐Abnormal
(c) Speech (articulation, aphasia, agnosia) Grossly ☐Normal
☐Abnormal - Specify Dysarthria ☐
Aphasia ☐

Reflexes (0-absent; 1-sluggish; 2-active; 3-very active; 4-transient clonus; 5-sustained clonus)

Deep	R	L	Deep	R	L	Other	R	L	Abnormal	R	L
									Babinski		
Biceps			Patellar								
Triceps											
			Achilles								
Remarks											

MENINGEAL IRRITATION Spurling Maneuver of Neck ☐Normal ☐Abnormal
this section is unnecessary ☐R ☐L ☐Both
in light of the thorough head & neck exam. Straight Leg Raising ☐Normal ☐Abnormal ☐R ☐L ☐Both

NERVE STATUS (tenderness, tumors, etc.) — Much too broad and open-ended.

SENSORY SYSTEM (tactile, pain, vibration, position. If positive sensory signs are present, summarize below and indicate details on Anatomical Figure, Std. Form 531)

Light Touch ☐Normal ☐Abnormal
Pin Prick ☐Normal ☐Abnormal (Map on Anatomical Figure)
Vibration (at ankle, 128 hz tuning fork): ☐Normal ☐Abnormal ☐R ☐L ☐Both
Position (Great toe): ☐Normal ☐Abnormal ☐R ☐L ☐Both

CRANIAL NERVES

I R Smell ☐Present ☐Absent
L Smell ☐Present ☐Absent

II Fundus R Normal ☐ Abnormal ☐ Disk Pallor/atrophy
☐Exudate ☐Papilledema ☐Hemorrhage

Fundus L Normal ☐ Abnormal ☐ Disk pallor/atrophy
☐Exudate ☐ Papilledema ☐Hemorrhage

Fields (to confrontation)
Right ☐Normal ☐Abnormal Left ☐Normal ☐Abnormal

III Normal ☐ ☐Abnormal - Specify
IV
VI Pupils-Size (mm) Equal ☐ Unequal ☐ Difference mm____
Shape, position Round ☐ Other ☐ ☐R ☐L
Light, Reaction Normal ☐ Abnormal ☐ ☐R ☐L
Position of Eyeballs

Movements R L

Nystagmus Rotary ☐ Horizontal ☐ Vertical ☐
(Draw position)

Ptosis R☐ L☐

V Motor R Clench Jaw - Symmetric ☐ Deviated ☐ R☐ L☐
L

Sensory R Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐
L Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐

Corneal Reflex R L

VII Motor R Normal smile ☐Yes ☐No Palpebral Fissure ☐Yes ☐No
L Normal smile ☐Yes ☐No Palpebral Fissure ☐Yes ☐No

IX Palate and Uvula
X Movement Normal ☐ Deviation to ☐R ☐L

Palatal Reflex R ☐Normal ☐Abnormal
L ☐Normal ☐Abnormal

XII Tongue-Protruded-Central ☐ R☐ L☐
Atrophy ☐No ☐Yes

MENTAL STATUS - This mental status test appears to be inappropriate, or at least much less appropriate and less standardized than the standard mini-mental exam.

Oriented to person☐, place☐, and time☐

Serial subtraction of 7 from 100, etc., number of errors _____

Number of 5 unrelated objects remembered after 5 minutes _____

Number of past 10 presidents remembers _____

Abstraction☐normal☐abnormal - specify

OTA - June 11, 1992

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta, Georgia 30333
FTS 236-4111

June 25, 1982

Mr. Maurice LeVois
Director, Agent Orange Research
and Education
Veterans Administration
810 Vermont Avenue, N.W.
Washington, D.C. 20420

Dear Maurice:

Enclosed is the Science Panel review of the VA Epidemiology Study Protocol. Also enclosed are the original comments of the individual Science Panel members. We are not maintaining these original comments in our files but trust that they will be available from yours should you need them for any specific purpose.

Sincerely yours,

Vernon N. Houk, M.D.
Chair, Science Panel
Agent Orange Working Group

Enclosures

cc:
Science Panel members

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta, Georgia 30333

VETERANS ADMINISTRATION EDPIDEMIOLOGY STUDY PROTOCOL
Dated April 28, 1982

The following is a concensus review by the Science Panel of the latest revision of the "VA Epidemiology Study Protocol" dated April 28, 1982.

The revised document shows major effort in some areas in response to reviewers' comments; however, the task of providing a revised protocol has not been completed. This leaves the problem of getting the revised protocol written and, more importantly, leaves numerous critical decisions up in the air. The revised document responded to many comments of the reviewers that several methods "could" be used to deal with the problems raised, but did not choose one solution for each problem, defend it, and incorporate the appropriate methodology in a revised protocol. This must be done by another party and will require another round of review.

It was suggested in the document that many problems raised by the reviewers be tested. It is of concern that detailed methodology for such testing and criteria for decision making were not provided. Each problem to be tested in the pilot study requires detailed design and a final protocol for the pilot study must reflect these specific situations in its methodology including clear criteria for the decision making.

Questionnaire and medical examination portions of the document have been improved (but not shortened) by reorganization and the inclusion of many detailed modifications. Table 1 assists in recognizing the expected medical outcomes based on animal and human data. Table 2 provides a good topical breakdown of the questionnaire items. They do not provide, however, a suggested list of abnormal conditions to be measured, the items in the questionnaire and medical exam to be used in their assessment, nor the estimated incidence of the various conditions needed as background for the data analysis. It is still unclear whether or how each of the many items will be used in the final analysis, and since the items to be collected are so numerous, nonessential and nonusable items still require identification and removal.

Specifically, the physical examination, questionnaire, and laboratory tests appear to be fishing expeditions. The response to our previous review that data collected for this study be only that necessary for the study and that are subject to careful standardization and analysis is inadequately addressed.

The questionnaire, in addition to being too diffuse, has many open ended questions and questions that suggest a specific response. The reproductive questionnaire is incomplete. It is the universal experience that incriminating questions (with identifiers) about illicit drug use are not honestly answered, are harmful, and probably would not be cleared by a panel reviewing appropriateness of the questionnaire.

There is vagueness in some of the responses to the reviewers' comments on epidemiologic concerns. Probably because a revised detailed protocol was not produced, it is still unclear what methodologies or criteria will be employed to meet the following problems:

1. A method of recruitment which will ensure comparable response rates from cohorts.

2. Compensation for the participating veterans.

3. Criteria for comparability of laboratory tests from various centers.

4. Methods of notification and followup of medical abnormalities.

5. Methods for "blinding" investigators.

The decision on the choice of exposure index has already been made by the Science Panel to reflect the proposal made by Dr. Bricker and Mr. Christian. The decision on inclusion of the third cohort is recommended by the Science Panel to be left open at this time and that DOD proceed with establishing such a cohort.

Several new suggestions are made in the revised document. Obtaining the assistance of a public relations officer seems desirable. However, the suggestion (page 51) that routine credit checks might be run on participating veterans seems without merit and likely to invite public outcry.

In summary, the present document has provided a much better organization for the demographic and medical assessments and further insights into many problems raised by the reviewers. However, no final protocol was produced, thus leaving many critical questions unanswered.

Vernon N. Houk, M.D.
Chair, Science Panel
Agent Orange Working Group

6/25/82

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date May 24, 1982

From Research Medical Officer
Center for Environmental Health

Subject Comments on the Latest Revisions (April 28, 1982) of the Agent Orange Epidemiologic Protocol

To Vernon N. Houk, M.D.
Chair, Science Panel
Agent Orange Working Group

Specific Comments

1. This document does not represent a revision but rather a rebuttal of the criticisms that have been made.

2. The overall study has now been estimated to last 5-1/2 years (page 1). This appears to this reviewer to be highly optimistic.

3. On page 5, the validation of exposure of individuals is discussed. Even if such validation was made, it would only be very crude. It is still not known how much each individual absorbed. Inhalation is greatly dependent on particle size of the sprayed material. Dermal absorption is influenced by weather conditions, cleanliness, different areas of the skin. Ingestion would depend on whether food was contaminated. Because of variation in the susceptibility of individuals within reason, somebody having received less of a dose might show an effect while somebody with a higher dose may not.

   For all of these reasons it seems to me that establishing a dose for each individual is an exercise in futility. The length of exposure will be useful, but it must be remembered that some with longer exposure may have received less of a dose than some with less exposure.

4. It is not clear (page 5) who the coordinating center investigators are and what their role is.

5. Page 6, last paragraph, is based on the assumption that a selection bias existed for service in Vietnam. What is the basis for this assumption and what is the selection bias?

6. Page 13 - Pilot Study. If the pilot effort is only to establish whether it is possible to conduct the outlined health study at all without interpreting the data, then a random sample is not needed. If, on the other hand, this is to be considered as a "mini-study" for which results will be interpreted, then a random sample is needed. This would mean that the entire cohorts would have to be established first, contacted whether they would participate, and then a random sample would be selected. This would greatly delay the study. I do not see the necessity for the latter approach.

7. Page 37. It is important to get information on tropical infections, particularly since it has been implied that TCDD affects the immune response.

General Comments

The study as it stands is a fishing expedition with very little focus. The questionnaire will be very difficult to code in many of its aspects. Many of the laboratory and other tests will yield very little, such as chest x-rays, ECG's. Others, such as the examination of semen and nerve conduction tests have not been very well standardized in the general population and will be very difficult to interpret. The cost of this entire undertaking will be enormous. Before any further decisions are made about this study, the following questions should be answered.

1. How much money is available for this study?

2. How can the present proposal be trimmed to give maximum information with a minimum of tests?

3. Only information that can be analyzed should be collected and computerized. What information really needs to be collected?

4. Could some of the proposed tests be done later on selected smaller subgroups?

In summary, I feel that the overall study is too ambitious and needs to be reduced to something that is manageable. It needs to be established whose responsibility this is: the Veterans Administration? the present contractor? or a committee?

Renate

Renate D. Kimbrough, M.D.

Bates 4-9

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D.C. 20301

HEALTH AFFAIRS

3 June 1982

Vernon N. Houk, M.D.
Chair, Science Panel, AOWG
Acting Director
Center for Environmental Health
Centers for Disease Control
1600 Clifton Road, N.E.
Atlanta, Georgia 30333

Dear Dr. Houk:

This letter is in response to Ms. Maureen Corcoran's memorandum of May 17, 1982 in which she requested our comments on the third version of Dr. Spivey's protocol be forwarded directly to you.

The following comments are provided with respect to the sections as indicated:

VFW Review, Pg. 3, Par 6: We support the views of the VFW that officers and regular enlisted personnel be included in the study. The cohort selection planners at DoD have already enlarged our data element columns to include differentiation between officers and enlisted personnel, and added another column to list number of tours in Vietnam. The cohort selection process will have to be accomplished before we can be absolutely sure that sufficient numbers of officers and multiple tour personnel can be located in the two Vietnam exposure categories.

AOWG Review, Pg. 5. 1st Para: Dr. Spivey still does not understand the details of the methodology proposed by Dr. Bricker, even though it has been discussed with him. The Bricker methodology after establishing that a unit (e.g. Company) has a high exposure frequency for a one year period, makes the listing of each time of exposure by date, UTM coordinate, and type of herbicide for that unit. Next we will then go into the morning reports which list all personnel for the unit. Each and every person assigned to the unit for the entire period of observation (1 yr) will then be tracked through time to see if he was present for duty and with his unit on each and every day that the unit was exposed to either Ranch Hand spraying, perimeter spraying, or in close proximity to a Ranch Hand herbicide dump or other accident. Finally, each person in that unit will be listed as to the number of exposures he personally had to Ranch Hand spray missions, perimeter spraying, and herbicide dumps or other accidents. People not found to be present with their unit when it is close to a Ranch Hand mission will not be counted as exposed to that incident. The difference between Dr. Spivey's methodology and Dr. Bricker's is in how you reach the end point -- individual

cumulative exposure. We believe the Bricker methodology is much more cost-effective and does not degrade the eventual cohort selection process in any way. Dr. Spivey's comments in the first paragraph are thus irrelevant to the problems at hand. Dr. Spivey missed the point entirely in his second paragraph. Never was there any intention to cancel the selection process if high numbers of persons on the agent orange registry did not appear in the herbicide exposed or non-herbicide exposed cohort name lists. Rather it was considered as an interesting scientific comparison to find out for our own benefit, and only ours, just how many persons on the registry did turn up in the two cohorts who served in Vietnam. Dr. Spivey is jumping to conclusions when he suggests that we had seriously proposed an hypothesis at this early stage when certainly no conclusions can be drawn at this point. However, in the long run, it might prove very beneficial from a public relations standpoint if much later in the VA epidemiological study we could state with certainty that either a certain number or a certain percentage of the Veterans who were in the agent orange registry were considered in our exposed cohort listing. It might be much more meaningful to the veterans associations.

AOWG Review, Pg. 6, 1st Para: Generally we agree with Dr. Spivey's recommendations concerning the need to maintain double blind security of the cohort lists. We feel this is a very important and critical aspect of the entire study, security of the cohort lists must be protected and access to either unit or name listings be limited to a very restricted number of persons in the Army Agent Orange Task Force who will generate the initial lists.

AOWG Review, Pg. 6, last response paragraph: We continue to support the utility and necessity for a non-Vietnam cohort just as the Australians have used. We seriously doubt that enough "cancelled just before shipment" units can be found to make up the 12,000 member cohort. We believe that comparably trained infantry combat units who were trained and then rotated to European combat assignments would meet the necessary qualifications for able bodied soldiers who might have been sent to Vietnam. We believe that the non-Vietnam cohort will provide the base-line data as to the health of the typical soldier who served during that period of time and that the non-Vietnam cohort may then be valuable as a comparison base to the "B" cohort consisting of troops who served in Vietnam but were not exposed to herbicides. When we do the study, why not do the whole study and find out, as some veterans claim, that just service in Vietnam, without herbicide exposure, deleteriously affected their long term health. What if both the herbicide exposed in-Vietnam cohort and non-herbicide in-Vietnam cohorts have similar health problems, how do you compare these problems if we do not have the third cohort of troops who were not herbicide exposed and were not assigned to Vietnam? We should provide all of the relevant facts with one pass through the study records and resolve the question to the best of our scientific ability.

OTA Review, Pg. 25, a. Cohort Selection: Apparently our briefing to the OTA did not succeed in making the point that the use of the morning reports (listing all individuals) would establish, on a day-to-day basis, whether a particular person was present or absent from the unit when it was exposed to a herbicide. We have already done this in the preliminary battalion studies last year; it is a time consuming process but gives a much higher degree of assurance that the individual soldier was exposed. We intend to do just such a fine personnel search on all exposed and non-exposed selected Vietnam units. Names of personnel assigned will thus be developed showing the numbers of exposures that each person experienced by classes of exposure (Fixed Wing Spray track, perimeter spraying, herbicide dumps or ground accidents) further divided by types of agent (Blue, Orange, or White). Since we already plan to accomplish a listing of name-exposure the OTA comments and Dr. Spivey's response are not pertinent.

OTA Review, Pg. 37, UCLA 3rd Para response: We disagree with the UCLA recommendation that tropical disease and parasitic disease questions should not be included. We support the recommendations of the OTA especially in the light of the recent publicity raised by the Dow Chemical company concerning possible latent infections caused by Pseudomonas pseudomallei. There is a further possibility of other parasitic diseases existing in our Vietnam veteran population. Why not try our best to find out what their problems really are?

OTA Review, Pg. 48, UCLA 4th Para response: The preceding paragraphs fairly well discuss the perceived exposure on the part of the veteran, however, no discussion is made concerning the possibility of having a large number of false positive reports simply because the veterans may have been confused by anti-malarial insecticide spraying from fixed wing and rotary wing aircraft which they may have believed to be herbicide spraying.

OTA Comments on Questionnaires, Pg. 50, page 10 comments: We feel that the point made by the OTA committee is very important concerning agricultural chemical exposures. We do not agree with the UCLA response as probing questions along this line could be most significant in determining subsequent heavy exposure to herbicides and other chemicals before or after service in Vietnam. For instance, personnel who were absolutely not exposed to herbicides while in Vietnam might be manifesting symptoms the same as those found in Vietnam exposed veterans and there is no reason to compensate persons exposed to dangerous chemicals while not serving in the military service. These exposure facts should be otained if at all possible.

Veteran Questionnaire for Agent Orange, Ques. 27, Pg. 13: We believe that unless the individual was directly involved in the loading or handling of herbicide spray equipment that it would be highly unlikely that he would be able to accurately identify a herbicide or insecticide. There is no way by visual means to identify what type of herbicide was being sprayed by either a helicopter or C-123 aircraft. This seems to be a useless question unless the person was a chemical handler or loader.

Ques. 28, Pg. 14: Why do they only ask for the names of defoliants and weedkillers? Back-pack and truck spraying may also have been used for insecticide spraying against mosquitos. Why not ask all of the questions?

Ques. 29, Pg. 15: Why not ask: "Did you ever handle drums of insecticides?" Other toxic chemicals were also used in Vietnam and were stored and shipped in 55-gallon drums. Why not ask a more generalized question about: "Did you handle any other toxic chemicals and if so what were they?" These shipment containers usually have the chemical name on the box or container.

Ques. 30, Pg. 16: Ask the individual if the spraying aircraft was a twin-engine C-123 and was he able to tell if it was silver colored or camouflaged? Insecticide spraying aircraft were always silver in color as the insecticide destroyed the paint on the aircraft.

Ques. 31, Pg. 17: Once again the average "G.I." is not likely to know the name of the substance that was sprayed. For this question, why not ask if there were any immediate physiological effects such as eye irritation, difficulty in breathing, odor, disorientation, upset stomach, cramping, or dizziness?

Medical Release Form, follows Pg. 20): They still have not corrected the "Service Record #," there is no such thing. We presume they mean his Military Serial Number which can be quite different from the Social Security Number. They also should be sure to get any alpha prefix or suffix to the serial number.

Card #14-15: This needs to be greatly expanded to cover many other toxic chemicals to which he may have been exposed before or after military service.

Medical History Questionnaire:

Ques. 4C., Pg.3: Why not include burns and puncture wounds from punjai stick traps instead of knife wounds?

Ques. 12 B., Pg. 10: If he does not know the drug, why not ask the color and size of the pill and how frequently taken and whether it caused gastric distress?

Ques. 39 through 45, pgs. 17-21: A confirmed drug user would probably never answer these questions in the affirmative to an interviewer especially when his name is known. It is self-incrimination to a witness. These questions would only be valid if given in the blind and anonomously. Do we really think the veterans will be that trusting when answering a questionnaire from the Federal government?

Ques. 91, Pg 59-62: Medical terms will not be understood by the average person, why can't these be simplified?

Ques. 92, pg. 63: Highly technical medical terminology still used, it will not be understood by the veteran, perhaps not even by a physician.

Ques. 104, pg. 81: Why did they not try to find out from the series of questions beginning at 104 whether the man was able to father and had fathered children before going to Vietnam and then after returning from Vietnam whether he was or was not able to father a child and whether he had tried to have more children. It would seem to be important to find out if there was a change in his procreative abilities subsequent to service in Vietnam.

Veterans Questionnaire Hand Cards, Card #49: We very seriously doubt that the average veteran will know the diseases listed in items G. through K. Probably some nurses and physician assistants may not either.

Card #91-92: Most if not all of the diseases listed here are not commonly known by the average man-on-the-street or probably most veterans.

Spouse Questionnaire for Agent Orange:

Ques. 1.: Why not ask for her maiden name also?

Ques. 17-23, pgs. 9-13: A confirmed drug user would probably never answer these questions in the affirmative to an interviewer especially when her name is already on the questionnaire. It is self-incrimination to the witness interviewer.

Ques. 37, pg. 22: Question asks: "Have you ever taken any of the following types of medications regularly and, if so, when? The last item in the following listing is "Spermicides." How do you take those orally? Do they mean birth control pills? We doubt that.

General Comment on Spouse Questionnaire: Why not ask if she has had any elective abortions and the reasons for same? Why not ask if she, herself, had ever served in any of the military services and if so, for what period and where?

Spouse Questionnaire Hand Cards: Card #13D-14: This is a very cursory treatment of the many possible toxic chemical substances to which the spouse may have been exposed to at the work place or in the pursuit of certain hobbies. It should be expanded and made specific for dangerous chemicals to help in her recall process.

General Comment on both Veteran and Spouse Questionnaires: Why not ask if either the husband (veteran) and/or spouse is receiving any disability payments from any Federal or State agency to include the VA, Military Services, or Workman's compensation?

P. A. Flynn

Peter A. Flynn
Captain, MC, USN
Senior DoD Member
AOWG Science Panel

To: Vernon Hauk, Chairman
Agent Orange Science Panel

From: Carl A. Keller, NIEHS/NIH

Subject: Review of Proposed Protocol for epidemiological study of ground troops exposed to the herbicide Agent Orange, from UCLA.

In as much as the proposed protocol is in the form of a paragraph-by-paragraph response to reviewers' comments on the previous draft, which I do not have in hand, my comments are in the same format. Reference will be made to pages and paragraphs of the proposed protocol.

Pages 1-4		I have no comments and agree with contractor.
Page 5	Para. 2	Current procedures for cohort selection being developed by staff of the D.O.D. Agent Orange Task Force already take into account individual's presence during unit exposures.
	Para. 3	I agree with contractors' concern that validation via comparison with VA Agent Orange Registry not lead to abandonment of the study.
Page 6	Para. 1	I agree that someone with major responsibility for this study should be involved with criteria for selection and comparability of cohorts as is already underway.
	Para. 2	I agree that some method for indicating that an individual is in a given cohort is necessary in order to do any meaningful analysis.
	Para. 4	If units scheduled to, but not sent to, Vietnam can be identified, this should be pursued. At the very least, non-Vietnam veterans who served out of the country should be selected, as is currently being done by D.O.D.A.O.T.F.
Page 7	Para. 1	I disagree with contractors' concern for comparability of a non-SE Asia Veterans group as I am not presently aware of selection bias related to area of service. This issue is currently being investigated by D.O.D.A.O.T.F.

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From: Carl A. Keller, NIEHS/NIH CAK

Para. 3 I agree with contractors comments.

Para. 5 Physician cooperation will depend on the extent of intended validation. I would like to see more information on this issue, i.e., what type of validation was being sought in contractors' previous experience and what type and amount is being sought in the present situation.

Page 8 Para. 2 I think separation of the questionaire into two parts is a good idea, but I am not convinced that the questionaire must be administered in the examination center nor that not doing so will result in an overall reduction in participation rates. While I do not feel that a two hour questionaire is overly long, the contractors did not address the question of the necessity and utilization of the information to be obtained by the submitted instruments.

Page 9 Para. 2 Contractors' response to reviewer concerns about the psychological and neuropsychological instruments indicates some disdain for these concerns and does not address the question of appropriatness of these instruments for the intended population.

Para. 4 I agree that a check-off list is an appropriate way to standardize the protocol for a physical examination, but contractors do not indicate how much time will be required to complete the examination. I would also prefer the opinion of a review board of examining physicians in terms of the medical conditions to be determined during the physical examination.

Para. 6 I do not agree with contractors' statements that standardization of laboratory procedures can be accomplished within the proposed pilot or study.

Page 10 Para. 2 A standard protocol must be used for the study. Additional information (not to be used in the study) can also be obtained in keeping with good medical practice and as a service to participating veterans.

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Para. 4 I agree with contractors.

Para. 5 Incompleteness of the National Death Registry is negligible now and thus should be adequate for future follow up to death. The major problem with this registry as far as the proposed study in concerned is that it only started in 1979!

Page 11 Para. 3 I agree that information regarding cohort selection should be made available to participating veterans following data collection and initial analysis.

Para. 5 I do not recall the details of the basic mechanism for follow-up of abnormalities from the draft protocol. However, I doubt that this is the responsibility of the contractors and the issue has been raised.

Page 12 Para. 5 I am not sure that "later follow-up from the study to assure that appropriate medical attention was obtained" is the responsibility of the study!

Page 13 Para. 1 Informing veterans of findings is the responsibility of the VA.

Para. 3 I think that the number of subjects to be included in the pilot should be reconsidered in terms of what is to be accomplished during this phase of the project.

Para. 4 I disagree that the pilot subjects need be a random sample of the study cohorts. What is necessary is that they be representative in specific ways of the study populations. One way of accomplishing this is to choose a random sample, but this is quite inefficient.

Para. 5 I agree with contractors that adequate numbers of subjects be included in the pilot phase at each examining center. However, I also feel that all potential examining centers be utilized in the pilot. I think the best solution will be to select those centers around the country which will be used in the

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study and include them in the pilot.

Page 14 Para. 2 It is not clear what "effects" are to be considered. For example, are the sample size considerations based on diagnostic categories or on individual signs and symptoms?

Page 16 Para. 4 Although contractors agree with statements submitted by OTA reviewers, they do not state what they agree with. Decisions on these check points must be made before the study is intiated. A much more detailed account of these issues must be developed.

Page 17 Para. 2 Some procedural timetable should have been developed, including who will serve in what capacity, and the responsibilities of any special oversight group.

Page 19 Para. 3 A detailed description of outcomes, the criteria to be used in their determination, and the expected number of affected individuals under the null hypothesis are needed in order to base realistic sample size ~~+~~ under the null hypothesis determinations to address the limitations of the proposed study.

Page 22 Para. 3 I agree with contractors and also caution that the usual load of HANES examinations would need to be substantially increased.

Page 25 Para. 4 An assessment of misclassification from the use of the group method of exposure estimation is being done.

Page 26 Para. 4 It is reasonable to expect that a comparison of health outcomes among exposed and non-exposed Vietnam Veterans should help to determine whether exposure to Agent Orange is responsible for poorer health. However, since many, if not all, of the proposed health outcomes can be caused by other and unknown factors, it would be unfortunate if the proposed study did not include a comparisons with non-Vietnam combat veterans to enable the assessment of possible health effects of other exposures in Vietnam. At present it has not

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been and may not be possible to determine whether significant chemical exposure was experienced by ground troops in Vietnam in most cases.

Page 28 Para. 3 A sample of non-respondents should be diligently pursued in order to ascertain their characteristics regardless of differential response rates.

Page 29 Para. 1,2 Certainly some information needs to be collected on deceased veterans. A decision on what information to collect will be neccessary before the determination of how to get it.

Page 33 Para. 1-3 I agree that open ended questions are generally not very useful during the analysis of epidemiological data, although they can afford an opportunity to cover material which the respondent feels should be included and may enhance the thoroughness of the study.

Page 37 Para. 1-5 There still needs to be a definitional statement about how each segment of the questionaire (the medical history part) and the medical examination relates to outcomes of interest. This should be done before even the pilot is initiated, and refined during the pilot phase. The contractors did not respond to this important issue.

Page 40 Para. 1-5 There is no mention of problems of standardization of laboratory procedures or results.

Page 41 Para. 2 There seems to be some diagreement between contractors' and OTA view of what is "Americanized." Perhaps some examples should have been presented to clarify this "problem."

Page 43 Para. 2 I am unsure as to how much of the psychological battery can be justified if the focus is on the outcome of chemical exposure to Agent Orange.

Page 44 Para. 4 Certain outcomes, e.g. birth defects, cancer and liver disease should be verified in some way, and uniformly so for all study participants. Explicit

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ways of doing this could have been developed by the contractors.

Page 47 Para. 1-5
Page 48 Para. 1-6
A good discusion by contractors on the effective utilization of objective and subjective measures of exposure to interpret the relationship between exposure, belief and outcomes.

Page 50-60 all Para. Many of these items further increase the length and complexity of the questionaire and examination procedures.

Table I

A much more useful presentation of these lists would be to briefly document the effects reported in animals and humans and to provide a basis for the choices in the "Most Likely List" from these or other sources. In addition to the list, a method for determining the presence or absense of these conditions, or a specific diagnostic category should be included.

Table II

This table is essentially a justification for the items in the questionaire. The topics and reasons for inclusion, however, include a number of items not found in the "Most Likely List" and those listed as confounders do not include what conditions they would be considered as confounders of. Thus, this table is not very useful to the protocol for the study.

Other Forms

These forms seem detailed and complete although I think it is rather premature to comment specifically on their adequacy until it has been determined exactly what health conditions will be investigated.

Overall Comments

The contractors have responded to some, but not all, of the concerns expressed by various reviewers of the previous draft. Much work, however, remains to be done in order to incorporate this submission into the protocol and few specific changes have been explicitly indicated with the exception of additions to the questionaire and examination forms. The contractors have chosen

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to agree, or, in many cases, to disagree with various points raised by reviewers so it is not possible to evaluate their final offering as a procedural guideline to performing this study and analysing results.

The most serious deficiency in the protocol submitted so far is the lack of a specific listing of health outcomes which are to be determined via questionaire, examination and laboratory results. In addition, the confounders relevant to each outcome should be included in order to facilitate appropriate analysis for comparison of health outcomes in exposed and unexposed cohorts.

Finally, sample size estimations should have included the likelyhood for identifying significant increase in each of the listed health outcomes in order to determine the limitations of the proposed study. While it is not likely that any submission would have constituted a final study protocol, it should have been expected that an effort of this magnitude would produce a more useful procedural guideline than has been submitted by the contractors.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

June 9, 1982

Director, DSHEF5
Epidemiologist, IMSB

VA Epidemiologic Protocol Review

Vernon Houk
Director, Center for Environmental Health, CDC

The materials provided by the contractor show major effort in some areas in response to reviewers' comments, particularly in the questionnaire and the medical examinations. However, the task of providing a revised protocol has not been completed. This unfortunate circumstance produces the problem of getting the revised protocol written, but more importantly, the present situation leaves numerous critical decisions up in the air. The contractors responded to many comments of reviewers that several methods "could" be used to deal with the problems raised. Because the contractor did not choose one solution for each problem, defend it, and incorporate appropriate methodology into a revised protocol, this must be done by another party and will require an additional round of review.

The contractor suggested that many problems raised by the reviewers be tested in the pilot study. It is of concern that detailed methodology for such testing and criteria for decision-making were not provided. For example, if the two cohort selection procedures (Dr. Bricker's and the contractor) are tested in the pilot study, as the contractor suggests, consideration must be given to an appropriate method, possible changes in numbers needed in the cohorts, and criteria for deciding which method to use in the full study. Each problem to be tested in the pilot study requires detailed design, and a final protocol for the pilot study must reflect these specific situations in its methodology, including clear criteria for decision-making.

There is vagueness in some of the responses of the contractor to reviewers comments on epidemiologic concerns. Possibly because a revised, detailed protocol was not produced, it is still unclear what detailed methodologies or criteria will be employed to meet the following problems:

1. Choice of the "exposure index".
2. Decision on inclusion of the "third cohort".

3. A method of recruitment which will insure comparable response rates from the cohorts.
4. Compensation for the participating veterans.
5. Criteria for comparability of laboratory tests from various centers.
6. Methods of notification and follow-up of medical abnormalities.
7. Method for "blinding" the investigators.

The contractor has improved, but not shortened, the questionnaire and medical examinations by reorganization and many detailed modifications. The inclusion of Table I assists in recognition of the expected medical outcomes based on animal and human data, and Table II provides a good topic breakdown of questionnaire items. However, it is still unclear whether or how each of the many items will be used in the final analysis. Since the items to be collected are so numerous, non-essential items still require identification and removal.

Several new suggestions are made by the contractor. Obtaining the assistance of a public relations officer seems desirable. However, the suggestion (p. 51) that routine credit checks might be run on participating veterans seems without merit and likely to invite public outcry.

In summary, the responses of the contractor have provided much better organization for the demographic and medical assessments and further insights into many problems raised by the reviewers. However, no final protocol was produced, thus leaving many critical questions unanswered.

Marilyn Fingerhut, Ph.D.

Philip J. Landrigan, M.D.

Joseph Mulinare, M.D.
June 9, 1982

Review of VA Questionnaire and Examination Protocol

There are a number of issues to be addressed about this revised instrument. Taken as a whole, it is a comprehensive attempt to ascertain a large volume of information. It suffers in several ways, however, because of its large size.

The medical questions asked cover a very broad range of problems. This seems to be in keeping with the philosophy of UCLA to acquire a large amount of information to generate hypotheses. I don't feel qualified to judge what questions should be asked in the general medical interview. To ask appropriate medical questions to the group of veterans is the job of adult-medicine consultants. (See comments below, however, about "reproductive" section.).

The instrument is very technical. The list of diseases asked will elicit "yes", "no", and "what is that disease?", responses from respondents. Interviewers will have to be trained to properly pronounce these diagnoses (eg. card # 101) and be prepared to explain the diagnosis or accept "don't knows". Differentiation among diagnoses may be very difficult eg. "disc trouble", "sciatica", for the respondent. There is a question in my mind, how the interviewer will handle these problems?

The structure of the instrument requires revision. Open ended questions are in the instrument (eg, spouse Q27). Questions are asked in a biased manner - Q57 in the medical section asks about having headaches. The next question does not ask what these headaches may result from, but lead the respondent to the possible diagnosis of migraine. Another example of a

leading question is #46. Questions contain many possible diagnoses which may be mutually exclusive. Q94 asks about "fits, faints and funny turns". If the answer is yes to this question, the interviewer continues to ask about dizzy spells, but no further mention of blackouts, fits or funny turns is made.

Major outcomes are dealt with in varying degrees of adequacy. As listed, major outcomes include:

infection	Q13 - one nonspecific question about ear, nose, skin and eye infections.
Skin	Q49-54
Liver disease	Q84
Autoimmune	Q91-92 - very technical diagnoses to ask respondents
Nervous system	Q93-100
Reproductive	Q101-112
Emotional	Q120 - only one question dealing with a major concern of the veterans. Is this related to stress disorders purported by vets?

The reproductive questions are incomplete. The OTA criticisms were not addressed by U.C.L.A. in their responses nor in their revised instrument. Questions about birth defects should be made with each pregnancy. Question 104 asks about fertility. Since fertility may be exposure related, to help determine the effect of any exposure would require coordinating exposure history with eg. occupational history and with reproductive history. In addition, spermicides should be added as method of contraception, Q104J.

This instrument is still in its development stage. It will require a concerted effort to finalize the questions. Decisions must be made about who will administer the instrument; whether many of the questions are too technical. If the pilot study uses lay interviewers, attempts should be made to optimize understanding of the questions in the most basic layman's terms. This is with the understanding that probes and interpretation will not be possible by the nonmedical interviewers who will be unable to define specific diseases.

This same concern can be addressed regarding the physicians who will be performing the physical examinations. It seems a decision should be made whether a small group of specifically trained physicians will conduct the exams or a cadre of physicians from institutions who have general medical training. The diagnosis and subsequent interpretation of clinical findings may require stringent criteria for any form of analysis, depending on which mode of examination is used.

In my review of the instrument I had a number of questions about specific parts of the instrument.

1) p2. Is military service number being obtained in another part of the interview?

2) p12. Does "company designation" include Division, Battallion, Brigade, etc"

3) p16. Is a question about binge drinking required?

4) p17. What does "regularly" mean with regard to marijuana use?

5) p79. Should herpes be added to the list of STD's?

6) p94 Q112f. Asks for serious problems in mother's family, is there a need to delineate those problems, if the response is yes?

Spouse Instrument

1) p8 Q16. Question should be split - actually two questions in one. These potential etiologies for adverse outcomes should be correlated to specific pregnancies of vet or spouse. Biological hypotheses would require eliminating possible spouse exposure as a confounder, esp. for reproductive failure or adverse outcomes.

2) p10-13. Questions asked for "regular" use of drugs. What does regular mean? How will it be analyzed?

3) p28 Q46. It is very difficult for respondents to deal with stillbirths as a pregnancy outcome. Many will know if birth defects were present. However, few will know birth weight and length. These questions about birth weight can be very sensitive and may have not usefulness in analysis.

4) p29 Q47. This question does not take into account time drugs were used during pregnancy, pattern changes in use of the drugs during pregnancy.

Summary:

The instruments presented for review have need for more work and revision. Development time for the instruments should be included in any future project plan. As it stands, this would not be an adequate instrument because of its structural and content deficiencies. A finished product from these preliminary instruments would require more investment of time and effort.