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Author

Corporate Author

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Young

2 JUN 1980

Response to the NAS Report Re: The Air Force Study of Personnel Exposed to Herbicide Orange

SAM/CC

Herein the principal investigators of the Air Force Protocol: "Epidemiological Investigation of Health Effects in Air Force Personnel Followup Exposure to Herbicide Orange," response to the National Academy of Sciences (NAS) Panel Critique of that protocol. The Air Force protocol was issued to the NAS panel members on ^{28 November} ~~December~~ _____, 1979; formally reviewed on the panel for three hours on December 19, 1979; and the NAS Panel report and attending press release was issued to the Air Force and public on May 6, 1980. This response is organized into General, Specific, and Summary Comment Sections for ease of review.

General Comments:

Although the NAS Panel report, pg ii, cites that panel members. . . "were chosen for their special competences and with regard for appropriate balance," the absence of the panel biostatistician seems to contravene this claim. It is axiomatic that the central issues of any epidemiologic study focus on the biostatistical considerations of experimental design and data capture, analysis, and interpretation. The lack of a biostatistician on the NAS Panel, and resulting lack of substantive discussion on biostatistical concepts during the 19 December review, led to considerable undervaluation of a strength of the Air Force Protocol. Further, it is noted and can be verified, that during the 19 December formal review, the majority of panel questions dwelled upon aspects of the Mortality Phase of the study - a study phase

acknowledged by the majority of previous peer panelists to be the least important aspect of the whole epidemiologic study. In addition, it is noted that Dr. ~~John~~^{IAN} T. Higgins, University of Michigan Medical Center, was not present at the 19 December Panel Review as cited, pg iii, in the NAS Panel Report.

In introduction of the NAS Panel Report, pg 1, it is asserted that the Air Force made "extensive modifications" of the scientific protocol following their previous peer reviews. This assertion is not founded upon fact. Each of the previous independent reviews, to be sure, helpfully contributed to the detailed scope of the comprehensive study but in terms of proportional adjustments, not in terms of major study element deletions or additions.

Within the NAS Panel description of the proposed study, pg 2, incorrect reference is made to the Air Force investigator's development of "three independent study goals." Clearly within the protocol, the study goals are hallmarked as interdependent. This basic misperception by the NAS Panel is perhaps responsible for the tenuous thrusts and conclusions found later in the report on pages 4, 6, 8, 10, 11, 12. To reiterate, the "goals" are interrelated, to wit: The primary issue (goal) is health; are there adverse health affects and if there are, can they be causely attributed to occupational exposure to Herbicide Orange? The cause for this health study is political (Politikos, Gr = citizen) in that thousands of people (veterans and scientists) are alleging and promulgating ~~xxxxxxx~~ that attributable adverse health effects in fact exist.

The issue of compensation to veterans is a spinoff, ancillary consideration. Compensation is referenced within the Air Force protocol for two significant reasons: 1) Possible future compensation to exposed study subjects, but not to unexposed control subjects, constitutes an extremely powerful positive bias that must be acknowledged by profound scientific care (as may be found within the protocol), and 2) from a governmental perspective, if compensation to veterans is to be conditional upon scientific evidence, then the epidemiologic study design must be broad-based and comprehensive to incorporate the wide spectrum of veteran complaints, and must be conducted as quickly as reasonable to provide whatever scientific interpretations the data permit. Clearly, the United States Government and its Veterans Administration have prudently opted to await additional scientific evidence, from any reputable scientific groups worldwide, before awarding compensation. It is already within the statutory power of the Veterans Administration to award compensation to veterans today, and without one shred of scientific evidence from any epidemiologic study. Thus, the Government is not awarding instant compensation and apparently for two reasons: 1) The alleged health issue may be a substitute for the social issue of society's benign neglect of Vietnam veterans following an unpopular war, and, therefore, not reason for "Health Compensation," and 2) the award of health compensation without substantive scientific input may be precedent setting with respect to other equally troubling environmental exposure issues. It is obvious that data from any scientific study on herbicide health effects will be used by both proponents and opponents of the compensation issue.

prospective study. Thus, in a scientific context, the NAS Panel phrase of "as designed" is bankrupt. And in light of the introduction of the NAS Panel press release of 6 May 1980, "Citing major weaknesses' in design. . .," it is clear that NAS has disturbingly misled the American public to the detriment of the issue itself.

Specific Comments:

Because of the detailed comments of the NAS Panel majority and minority on three broad critique areas, specific response will be made to commentary within each area as well as to the summary recommendations.

I. Statistical Power of the Study

| A. | <u>NAS Majority</u> | <u>NAS Minority</u> | <u>AF Response</u> |
|----|--|--------------------------------|--------------------|
| | Little chance of detecting mortality effect within follow-up period (pg 5) | Nonconcur (Appendix pg 1,2) | Nonconcur |

AF Commentary:

This majority comment presupposes that the mortality effect of the herbicide is low, if existent, in the age ranges of the study cohorts, a notion which is a question of the study; this concept receives cogent review by the minority. Both majority and minority comments, however, reflect misperception of the length of the followup cited within the protocol. It is clearly stated (Protocol pages _____) and thoroughly intended by the principal investigators that followup study phases be projected in five year renewable blocks, subject to the advice of an outside monitoring agency and to the appropriate review by the Air Force Surgeon General. Five year blocks were chosen because the Air Force attempts to project resource requirements five years in

advance of usage. Intuitively, a minimum of 2 five-year periods past the initial followup phase would be required to observe the study cohorts in a period of the highest death rate (mean age projected, 65). These facts were emphasized verbally to the NAS Panel during the review but were apparently discarded.

| B. | <u>NAS Majority</u> | <u>NAS Minority</u> | <u>AF Response</u> |
|----|--|---------------------|-------------------------|
| | Panel conceived that study with limited followup would be incorrectly interpreted (pg 5) | No Comment | Non [^] concur |

AF Commentary:

Since the followup phase is not limited to exactly five years as perceived, the issue is moot. Further, no reputable scientific group would allow such an elemental error either in the literature or lay press.

| C. | <u>NAS Majority</u> | <u>NAS Minority</u> | <u>AF Response</u> |
|----|---|---------------------|--------------------|
| | Conduct additional power calculations at several Beta levels (pg 6) | No Comment | Concur |

AF Commentary:

More detailed power calculations are in progress. It is noted that since study is observational and uses the maximum number of exposed study members, power calculations cannot be used to ideally adjust the number of exposed participants. Thus, the NAS majority statement, pg 5, "Since statistical power is crucial to the flexibility of the study. . ." is incorrect.

| | | | |
|----|--|--------------------------------|--------------------|
| D. | <u>NAS Majority</u> | <u>NAS Minority</u> | <u>AF Response</u> |
| | (Find larger cohort) or follow study cohort for 20-30 years Post exposure (pg 6) | Concur (pg 3, Appendix) | Concur |

AF Commentary:

Exposure to Herbicide Orange in the Ranch Hand Group occurred 10-18 years ago. At the completion of the first follow-up five year block, postexposure will range from 16-24 years. As previously stated herein, additional five-year periods of follow-up have been contemplated and incorporated within the protocol.

| | | | |
|----|---|------------------------------------|--------------------|
| E. | <u>NAS Majority</u> | <u>NAS Minority</u> | <u>AF Response</u> |
| | Mortality analysis could not determine if AF personnel are at increased risk to cancer, etc (pgs 5, 6) | Nonconcur (Appendix pg 2,4) | Nonconcur |

AF Commentary:

The NAS majority conjectures that the herbicide effect, if it exists, is weak and therefore will not be detected with the current limited study population. The strength of the herbicide effect, if it exists, is, in fact, the subject of scientific inquiry. Further, the NAS majority notation ignores unusual career clustering that may be observed following environmental exposures, and considerably undervalues the prospective collection of both morbid and mortality data. The Air Force protocol well describes the overall power boundaries of the study, a fact paradoxically receiving the panel's commendation

"for careful consideration" (pg 7). Concepts of "increased risk" to both common and rare health events must await conduct of the study in order to be placed in proper perspective. It will obviously be a responsibility of the investigators to cite power calculations, confidence limits, etc., for all key study observations so that every scientist may make his own interpretation of the data. To be sure, cases clinical endpoints will be difficult to ascertain unless case clustering or broad based relative risks emerge, but this is an irreceivable circumstance imposed by nature and not by the design of the study.

AF Commentary:

The investigators acknowledge that improvements in the fertility analysis are indicated and desirable. Questionnaire aspects on fertility and reproductive outcomes are being appropriately expanded.

| H. | <u>NAS Majority</u> | <u>NAS Minority</u> | <u>AF Response</u> |
|----|--|---------------------|--------------------|
| | Integrate other exposed populations (Marines) into a coordinated study (pgs 6, 8, 9) | Nonconcur (pg 2, 4) | Nonconcur |

AF Commentary:

The NAS majority, through persistent overconcern on statistical power, fell into the trap of proposing the "integration" or addition of other "exposed" individuals (Marines) to the Ranch Hand group as a simplistic solution to suboptimal study power. This problem, which was well acknowledged by the NAS minority, merits significant discussion from several perspectives in order to highlight this surprising and sophistic proposal.

The Marine data cited by the NAS Panel (pg 9) were probably extracted from the Government Accounting Office Report #FPCD-80-23, 16 Nov 79, "U.S. Ground Troops in South Vietnam were in Areas Sprayed with Herbicide Orange." These data represent approximations of Marine strengths within distance and time parameters of Ranch Hand mission profiles (Herbs Tapes). Designation of exposure to Herbicide Orange for any given marine is highly tenuous for the following reasons:

GAO methodologies to obtain these data have not been verified.

The NAS majority's fascination with larger numbers and theoretically higher study power in the marine population also raises the issue of "degree of exposure." It is clear that a minimum estimate of one order of magnitude difference exists between exposure of the Ranch Hand population (exposed massively, via skin and respiratory routes, on a twice daily basis) and the probabilistic rare event exposure of the marines. From a three dimensional perspective, degree or magnitude of exposure must play the key role in power considerations. Hence, from the exposure context, the Ranch Hand population provides the most powerful opportunity to ascertain health impacts if they exist and erases the numeric advantages of the marine population.

In short, because of potentially overwhelming misclassification of the marine population, the substantial differences in degree of exposure, and the significant differences in host factors between the populations, they are clearly noncommensurable. To combine or "integrate" the two populations into a ~~simple~~^{SINGLE} study, as proposed by the NAS majority, would constitute incorrect epidemiology.

OVERALL IMPRESSION IS THAT THIS DOCUMENT WILL NEVER

LEAVE SAM. WHO WILL WRITE THE NAS REPORT? WE DONT KNOW HOW TO PLAY POLITICS - THE TONE OF THIS RESPONSE WILL PROBABLY TOTALLY REMOVE THE

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This is a TOTAL CATHARSIS - when do we go to work on this response?

? COVER LETTER
? OF NECESSARY
WE ARE PROBABLY
THE ONLY ONES
CONCERNED E.G. -

TONE IS ABRASIVE

Strength

RESPONSE TO NAS

GENERAL:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|-----------------------------|--------------------|
| 1. GOALS INDEPENDENT | NO COMMENT | NONCONCUR |
| 2. STUDY WEAKNESSES "AS DESIGNED" | NONCONCUR (AP, PGS 1, 4) | NONCONCUR |
| 3. EXTENSIVE MODIFICATIONS IN PROTOCOL AS RESULT OF PEER REVIEW (PG 1) | NO COMMENT | NONCONCUR |

RESPONSE TO NAS

| MAJORITY | MINORITY | AF RESPONSE |
|---|-----------------------------------|--------------------|
| 4. LITTLE CHANCE OF DETECTING MORTALITY IN FOLLOW-UP PERIOD (PG 5) | NONCONCUR (AP. PG 1,2) | NONCONCUR |

RESPONSE TO NAS

STATISTICAL POWER:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|----------------------|----------------------|
| 5. FOLLOW STUDY COHORT 20-30 YRS EXPOSURE (PG 6) | CONCUR (AP. PG 3) | CONCUR - IN PROTOCOL |

RESPONSE TO NAS

STATISTICAL POWER:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|-------------------------|--------------------|
| 6. STUDY WITH LIMITED FOLLOW-UP WOULD BE INCORRECTLY INTERPRETED (PG 5) | NONCONCUR (AP, PG 4) | NONCONCUR |

RESPONSE TO NAS

| MAJORITY | MINORITY | AF RESPONSE |
|---|-------------------|--------------------|
| 7. DO MORE POWER CALCULATIONS AT SEVERAL LEVELS (PG 6) | NO COMMENT | CONCUR |

RESPONSE TO NAS

STATISTICAL POWER:

MAJORITY

MINORITY

AF RESPONSE

**8. MORTALITY STUDY
CANNOT DETERMINE
INCREASED RISK OF
CANCER, ETC. (PGS 5, 6)**

**NONCONCUR
(AP, PGS 2, 4)**

NONCONCUR

RESPONSE TO NAS

STATISTICAL POWER:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|-------------------------|--------------------|
| 9. DIFFICULT TO JUSTIFY COMPENSATION BASED ON STUDY RESULTS (PG 6) | NONCONCUR (AP. PG 4) | NONCONCUR |

NAS RESPONSE

STATISTICAL POWER:

MAJORITY

MINORITY

AF RESPONSE

10. INADEQUATE PROVISION FOR
ASSESSMENT OF REPRODUCTIVE
OUTCOMES (PGS 9, 10)

CONCUR

PARTIALLY CONCUR

RESPONSE TO NAS

STATISTICAL POWER:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|-----------------------------|--------------------|
| 11. INTEGRATE (ADD) OTHER EXPOSED POPULATIONS (MARINES) INTO A COORDINATED STUDY (PGS 6, 8, 9, 12) | NONCONCUR (AP- PGS 2, 4) | NONCONCUR |

RESPONSE TO NAS

STATISTICAL POWER:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|---|-------------------------|--------------------|
| 12. IN MORTALITY STUDY INCREASE STUDY/CONTROL RATIO FROM 1:5 TO 1:25 (PG 12) | NONCONCUR (AP. PG 1) | NONCONCUR |

RESPONSE TO NAS

STATISTICAL POWER:

| MAJORITY | MINORITY | AF RESPONSE |
|----------------|---|-------------|
| 13. NO COMMENT | LEVEL OF EXPOSURE IN MARINES RELATIVELY LIMITED IN EXTENT AND DURATION (AP, PGS 2, 4) | CONCUR |

RESPONSE TO NAS

STATISTICAL POWER:

| MAJORITY | MINORITY | AF RESPONSE |
|---|-------------------|--------------------|
| 14. ESTABLISH BASELINE VALUES IN EXPOSED AND CONTROL GROUPS AND REPEAT IN 10 - 20 YEARS (PG 8) | NO COMMENT | NONCONCUR |

RESPONSE TO NAS

HEALTH INDICES:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|-------------------------|--------------------|
| 15. EVALUATION OF TOO MANY HEALTH INDICES, FOCUS TO 3-4 (PG 9) | NONCONCUR (AP. PG 3) | NONCONCUR |

RESPONSE TO NAS

HEALTH INDICES:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|---|-------------------------|--------------------|
| 16. DUBIOUS VALUE TO LOOK FOR PORPHYRIA OR CHLORACNE (PG 9) | NONCONCUR (AP. PG 3) | NONCONCUR |

RESPONSE TO NAS

HEALTH INDICES:

MAJORITY

AF RESPONSE

**17. EVALUATE SELECTIVE
ENDPOINTS WITH MORE
SENSITIVE TECHNIQUES
(PG 10)**

NO COMMENT

CANNOT COMMENT

RESPONSE TO NAS

CREDIBILITY:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|----------------------|--------------------|
| 18. ISSUES COULD BE RESOLVED IF STUDY CONTRACTED OUT (PG 11) | CONCUR (AP, PG 5) | NONCONCUR |

RESPONSE TO NAS

CREDIBILITY:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|---|-----------------------------|--------------------|
| 19. STUDY AS DESIGNED HAS SO LOW A PROBABILITY OF DETECTING AN EFFECT, EVEN IF ONE EXISTS (PG 10) | NONCONCUR (AP. PG 1,2,4) | NONCONCUR |

RESPONSE TO NAS

CREDIBILITY:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|---|-----------------------|--------------------|
| 20. INAPPROPRIATE FOR USAF OR DOD PERSONNEL TO COLLECT THESE DATA THEMSELVES IF PROGRAM PART OF ATTEMPT TO PROVIDE SCIENTIFIC BASIS FOR AWARDED COMPENSATION TO VA CLAIMANTS (PG 11) | CONCUR? (AP. PG 5) | NONCONCUR |

RESPONSE TO NAS

UNADDRESSED MINORITY COMMENTS:

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|-----------------|---|--------------------|
| 21. NO COMMENT | MAJORITY REPORT MAY CAUSE LONG DELAY IN STUDY AND NOT RESULT IN ANY MAJOR IMPROVEMENT IN DESIGN OF THE STUDY (AP. PG 1,4) | CONCUR |

RESPONSE TO NAS

UNADDRESSED MINORITY COMMENTS:

MAJORITY

MINORITY

AF RESPONSE

22. NO COMMENT

**IF STUDY PRODUCES NO
EVIDENCE OF SERIOUS
DISEASE, EXPOSED INDIVIDUALS
WOULD BE REASSURED
(AP. PG 3)**

CONCUR

RESPONSE TO NAS

UNADDRESSED MINORITY COMMENTS:

| MAJORITY | MINORITY | AF RESPONSE |
|-----------------------|---|---------------------------------|
| 23. NO COMMENT | GROUP RESPONSIBLE FOR STUDY APPOINT AN ADVISORY COMMITTEE OF STATISTICIANS AND EPIDEMIOLOGISTS TO REVIEW DESIGN AND DATA ANALYSIS (AP. PG 5) | CONCUR - IN PROTOCOL |

RESPONSE TO NAS

MAJORITY CONCLUSIONS AND RECOMMENDATIONS:

PGS 11-12

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|---|-----------------|-------------------------|
| 1. STUDY SHOULD BE REDESIGNED TO INCLUDE CONSIDERABLY LONGER FOLLOW-UP | CONCUR | CONCUR - IN PROTOCOL |

RESPONSE TO NAS

MAJORITY CONCLUSIONS AND RECOMMENDATIONS:

PGS 11-12

| <u>MINORITY</u> | <u>MAJORITY</u> | <u>AF RESPONSE</u> |
|--|------------------------|---------------------------|
| 2. IF STUDY REDESIGNED EVALUATE A LIMITED NUMBER OF MORBIDITY ENDPOINTS, EACH IN GREATER DETAIL | NONCONCUR | NONCONCUR |

RESPONSE TO NAS

MAJORITY CONCLUSIONS AND RECOMMENDATIONS :

PGS 11-12

| <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|--|-----------------|--------------------|
| 3. ANY REVISIONS OF STUDY SHOULD BE SUBJECTED TO OUTSIDE PEER REVIEW | CONCUR | CONCUR |

RESPONSE TO NAS

MAJORITY CONSLUSIONS AND RECOMMENDATIONS:

PGS 11-12

| | <u>MAJORITY</u> | <u>MINORITY</u> | <u>AF RESPONSE</u> |
|----|---|-----------------|--------------------|
| 4 | EXAMINE CREDIBILITY ISSUE IN VIEW OF PUBLIC PERCEPTION AND STATED STUDY GOALS | CONCUR | NONCONCUR |
| 4A | CONSIDER <u>ADDING</u> LARGER COHORTS (MARINES) OF EXPOSED AND UNEXPOSED TO THE RANCH HAND PROJECT | NONCONCUR | NONCONCUR |