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The Effects of Exposure to Agent Orange on Ground Troops in Vietnam

A report of a subcommittee appointed to review a protocol (dated January 22, 1982) prepared by the University of California, Los Angeles, at the request of the Veterans Administration

for

The Committee on Epidemiology and Veterans Follow-up Studies
Commission on Life Sciences
National Research Council

October 1982

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Summary of Recommendations

1. If any attempt is to be made to study health effects of "the Vietnam experience" more broadly than the exposure to Agent Orange, it should be made independently of the Agent Orange study.
2. Before a decision is made to proceed with the main Agent Orange study, there should be a formal review to determine the meaningfulness of the classification of study participants by exposure status and the views of interested parties should be ascertained and recorded.
3. A fully satisfactory method of selection of participants has not been described to the Subcommittee. This matter requires much further investigation and evaluation.
4. If an individual exposure index is calculated for each possible study subject, rather than two (high and low exposure) cohorts there should be three (high, intermediate, and low exposure).
5. The cohorts should be selected as several -- say four -- independent subsamples.
6. (a) Marines should be included if they can be identified in sufficient numbers for separate analysis and if they can be included in equal proportions to the total numbers in each cohort.
   (b) Air Force personnel should not be included.
   (c) Officers should not be included.

(d) Enlisted men with multiple tours of duty in Vietnam should not be included.

(e) Every effort should be made to include the crews and servicemen of Army-based helicopters used for spraying, as well as suitable non-exposed individuals from other helicopter operations.

7. Greater emphasis should be placed on the study of mortality in the selected cohorts up to the present and into the future.

8. (a) The current questionnaire and clinical protocols require considerable revision. They should take advantage of the expertise and experience expended on the design and the experience gained in the implementation of the protocols for the Ranch Hand study.

(b) The pilot study for the clinical investigation should not be initiated until findings from the Ranch Hand study are available. The Subcommittee was informed that data collection for the Ranch Hand study would be completed by September 1982.

(c) Findings from mortality analyses should also be used to modify the clinical protocols, if appropriate.

(d) The questionnaire needs particular attention.

(e) The protocols should be more focused toward known effects of exposure of humans or other species to dioxins.

(f) A tiered approach to clinical testing is recommended.

9. More attention should be paid to issues of quality control in the clinical examinations. The pilot study should include at least three examination sites.

10. The payment of incentives to participants seems reasonable and desirable.

11. Responsibility for the main study should rest with an academic-based coordinating center strong in biostatistics and epidemiology, with experience in multi-center collaborative studies and answering to a Steering Committee. The Steering Committee would include representatives of the participating units, which might be in academic or non-academic settings.
12. The present questionnaire and clinical protocol, and any subsequent drafts, should be made available to interested parties.
13. There should be representation of the socio-behavioral sciences in the planning and implementation of the study.
14. If this program goes forward, the funding required should not be diverted from the regular medical research budget of the VA.

Introduction

The Subcommittee had as its assigned charge to review and comment on the protocol prepared by the University of California, Los Angeles (UCLA), (Principal Investigator Gary H. Spivey, M.D., MPH) and, if appropriate, to make suggestions which might strengthen the protocol and improve the effectiveness and efficiency of the final study. The Subcommittee found its approach to this charge complicated by a number of circumstances:

(1) That some study must be done has been mandated by Congress, and it has been further mandated that the study should be "epidemiological" in nature and have as its goal the detection of "any long-term health effects in humans" (emphasis added) attributable to "exposure to the phenoxy herbicides (including the herbicide known as Agent Orange)..." (Public Law 97-72, Nov. 3, 1981 95 STAT 1061). The range of research designs that might be considered to approach the overall objective is therefore limited by the congressional mandate.

(2) The UCLA protocol already has been reviewed, modified, and reviewed again by at least two committees or panels (of the White House and of the Office of Technology Assessment), both of which had representation of scientific disciplines considerably broader than this Subcommittee, as well as by veterans' organizations. The reports of these review panels are available to the Subcommittee.

(3) Notwithstanding the UCLA protocol, the previous reviews of it, and the existence of this Subcommittee, the Veterans Administration (VA), with support from the Department of

Defense (DOD) in the selection of cohorts, is well along in the planning of a pilot study of Vietnam veterans directed to this issue, with a target date for initiation of January 1, 1983. The method of selection of the cohorts for the pilot study being used by DOD differs in important ways from that proposed in the UCLA protocol -- a change that is defended principally in terms of economy -- but it is not clear to the Subcommittee that the scientific implications of the change have been thoroughly explored.

In these circumstances, the Subcommittee considers that it would be of little service to prepare a detailed review of the UCLA document as written -- a document that is already worn around the edges insofar as it can be regarded as a blueprint for any likely action -- or to add its own voice to those who previously have reviewed the protocol in detail and whose recommendations are on record. Rather, the Subcommittee proposes to present its views (some solicited and some not) on certain broad issues which the VA and other planners of this study must face in the next few months.

First, the Subcommittee agrees with the UCLA investigators and other reviewers that, given the objectives, the most appropriate form of study design has been selected. It is proposed to identify cohorts (groups) of ground forces characterized as to relative level (or levels) of exposure to phenoxy herbicides during the Vietnam experience, to follow these cohorts with respect to mortality subsequent to their Vietnam service, and to measure many parameters of current health status. These parameters will be compared between the different exposure cohorts. This form of study is commonly

called a retrospective cohort or retrospective follow-up study and is appropriate when (a) the exposure of interest occurred in the past and is documentable and (b) a number of different possible health, or ill-health, outcomes are to be investigated.

The most frequent alternative approach to the study of suspected causal associations between environment and health is to select a group of individuals manifesting a disease that is hypothesized to relate to the exposure (the cases) and a group of individuals without that particular manifestation (the controls) and to compare the cases and controls with respect to frequency or intensity of past exposure. The range of ill effects alleged to result from exposure to Agent Orange (AO) is so broad as to make the case-control approach unfeasible if any substantial proportion of them is to be addressed. This is not to say, however, that some case-control studies may not be feasible and desirable; indeed, such studies may well produce more information -- and for fewer dollars -- than the all-encompassing cohort study. For example, there is evidence from non-military exposures that risk of soft-tissue sarcomas may be increased following fairly heavy exposures to phenoxy herbicides. A case-control study of soft-tissue sarcomas within the veterans population would almost certainly be the quickest and most economical way to determine whether these malignancies are associated with exposure to herbicides in Vietnam. Such a study would not, however, address the many other outcomes of herbicide exposure that can be hypothesized and which have been suggested.

Nevertheless, the Subcommittee will address principally the questions which have been raised with it and which the Subcommittee

had regarding the retrospective cohort study, since this is the subject of the UCLA protocol and current VA plans. The following issues are not in any discerned order of importance or priority.

1. Addition of a study of "the Vietnam experience"

In permissive (i.e., not mandatory) language, the 1981 Public Law states that "the Administrator (of Veterans' Affairs) may expand the scope of the study to include an evaluation of any long-term health effects in humans of such service (in Vietnam) that may result from other factors involved in such service, including exposure to other herbicides, chemicals, medications, or environmental hazards or conditions." This language has resolved into a debate as to whether, by adding a third cohort of servicemen without experience in Vietnam, the intent of this clause may be met by comparing the non-Vietnam cohort with the cohorts assembled for the AO study. Of the latter, the UCLA protocol and the VA currently envisage two -- one with high and one with low exposure to AO. The components of "the Vietnam experience" -- quite apart from the physical and psychological impacts of participation in combat -- are multiple. A partial list includes exposure to insect repellents, insecticides, water purification chemicals, antimalarial drugs, petroleum distillates including napalm, weapons residues, chemical weapons, beverage alcohol, illegal narcotics, liquid hexachlorophene soaps, immunizations, food contaminants, dioxin-containing pentachorophenol (for wood preservation) and a variety of viral, bacterial, fungal and parasitic diseases and their therapies.

The Subcommittee believes that the complexity of this "Vietnam experience" is such that it will likely never be possible to study

it in any meaningful way -- that is, a way that would permit linkage of specific health outcomes to specific components of the experience. Nor is it clear that a suitable comparison group with which to compare the health of the Vietnam veterans has been (or can be) identified. However, if it is decided to make an attempt to study the effects of the total Vietnam experience the Subcommittee strongly urges that it not be done through the over-simple expedient of adding a non-Vietnam cohort to the AO study.

The Subcommittee's reasons for this view are as follows:

(a) The AO study is itself very complex. Yet its complexity would be dwarfed by that of an attempt to study the Vietnam experience overall. There is a serious danger that the addition of the "Vietnam experience" component would jeopardize the already insecure scientific base on which the AO study rests.

(b) For a study of "the Vietnam experience", contrasting the experience of military ground forces in Vietnam with that of those in some other theater, the sample of Vietnam veterans should be selected in a different fashion from that required for the AO study. Two Vietnam cohorts representing the extremes of high and low exposure to AO are almost certainly not representative of all ground forces that saw service in Vietnam.

(c) The Subcommittee shall address later the desirability of focusing and shortening the medical history and clinical data collection instruments. More focused instruments -- which would be highly desirable for either study -- will be different according to whether one is looking for suspected effects of AO or of the total Vietnam experience.

For these reasons the Subcommittee recommends that the desirability and design of a study of the long-term effects of the total Vietnam experience be considered independently from the planning for the AO study.

2. Feasibility of the retrospective cohort study

For several years the retrospective cohort study was widely regarded as unfeasible -- principally because of the difficulty of assembling from existing records valid information on the exposure of individuals to AO and other herbicides. On the basis of preliminary work on the part of DOD, this view has now changed. Those responsible for the DOD record review now state that, not only will it be possible to identify individuals with presumptively high levels of exposure to AO, but that it should be possible to select a comparison cohort of low-exposure individuals from military units with combat and jungle experience similar to that of the high-exposure cohort. Consequently, the VA is planning to proceed with clinical examinations for a pilot study beginning January 1, 1983.

As noted above, a retrospective cohort design is an appropriate one when the exposure of interest occurred in the past and is documentable. Everybody understands and agrees that the documentability of exposure, or lack of exposure, is a sine qua non for this study. If the compared cohorts are not markedly dissimilar with respect to true cumulative exposure levels the study is unlikely either to reveal health effects that do exist or to satisfy the public that a valid search for such effects has been undertaken. The Subcommittee indeed questions the wisdom of proceeding with the pilot study until this issue is settled. So far as the Subcommittee

is aware, the DOD record review to date has concentrated on the identification of high-exposure individuals. The method depends on identifying individuals who receive a high exposure during a given time period (approximately one year), and presumably could be used similarly to identify individuals receiving low (or no known) exposure during comparable periods. However, the validity of the procedure remains essentially unevaluated.

A decision to proceed with the pilot clinical examinations may be justified on the grounds that the feasibility of this phase of the study is equally as critical to the main study as is the estimation of exposure and that a matter of such national priority and urgency warrants proceeding with both assessments simultaneously even though a failure in either one will argue against proceeding with the main study. There are certainly important issues of feasibility to be assessed for the clinical component of the study. For example, although the response rate in the Air Force's study of its "Ranch Hand" veterans who sprayed herbicide from fixed-wing aircraft has been extraordinarily good (of the order of 94 percent), this is a special group with a high esprit de corps; such a response rate cannot automatically be assumed for a more broadly selected group of veterans. A high participation rate in the clinical program is essential if it is to produce reliable results. Vigorous efforts must be made to ensure the cooperation of at least 75-80 percent of those invited to participate. If the participation rate falls short of this target or if the rates in the high and low exposure cohorts differ by more than 10 percent, considerations should be given to abandoning the clinical examination component of the program.

In addition, it must be kept in mind that a successful completion of the clinical pilot study is not alone a sufficient basis on which to proceed with the main study -- the issue of adequate separation of the cohorts by exposure level must also be addressed. Unfortunately, there appear to be no objective criteria on which to validate this separation. At a minimum, the criteria used to define the cohorts must be sufficient to convince those involved -- including the veterans' organizations -- that the separation is meaningful in terms of exposure. Documented assurance that the meaningfulness of the separation has been accepted by interested parties should be a prerequisite to a decision to proceed with the main study.

One suggestion for evaluating the validity, or at least replicability, of the exposure assessment has been that exposure measures as determined for the study from records (see Section 3, below) be compared with self-reported exposures to be elicited during the clinical examinations and questionnaires. While the possibility of error, and indeed bias, in self-reporting is evident, such a comparison would be an important part of the analysis of the pilot study data. An intermediate exposure cohort (see section 4) might be particularly valuable in this connection.

3. Assessment of exposures of individual veterans

The method of identifying veterans with relatively high levels of exposure to AO currently being used by DOD differs importantly from that recommended in the UCLA protocol. The protocol recommends that an exposure index -- a cumulative measure of the product of presumed level of exposure and time served at that level -- be

computed for essentially all Vietnam veterans, and that the high-exposure and low-exposure cohorts be selected from individuals at the top and bottom of a ranking by this index. The DOD procedure depends on first identifying military units (generally Companies) with probability of high exposure and then assembling the histories of individuals in these units. Presumably, a comparable procedure will be used to identify the low-exposure cohort. Officials of DOD estimate the cost of record review necessary to carry out the UCLA plan as $27-40 million, and of their own procedure as $3 million. The saving is clearly of consequence. However, the DOD procedure imposes certain constraints on the selection procedure, the consequences of which have not been fully explored. For example, an individual's cumulative exposure is estimated over a twelve-month period beginning with an arbitrary date (July 1). Consequently, individuals who began service in Vietnam in that particular month are more likely to be selected into the high-exposure cohort. It is not clear whether such temporal constraints are also intended to apply to the low-exposure cohort or, if it is, how this can be accomplished. There are probably other selective factors that a more detailed review than the Subcommittee has been able to undertake would identify. Even if such factors are not specifically identified it seems ill-advised to use a selection procedure that cannot be followed in an exactly comparable way for high and low exposure groups.

Since the protocol for the DOD selection procedure was not available in written form for the Subcommittee's review and because the time available for this review was limited, the Subcommittee cannot judge how comparable the selection procedure for the high and

low exposure cohorts will be. The Subcommittee notes, however, that the clinical examinations for this study are estimated to cost over $10 million, and may be much more. It would be false economy to choose, on the basis of its cost, a cohort selection procedure that jeopardizes the validity -- or even the appearance of validity -- of the study findings. This issue requires much further investigation before the final method of cohort selection is decided. It may be that an intermediate procedure can be identified which combines the advantages of the UCLA proposal with the (relative) economy of the DOD procedure. It does appear to the Subcommittee that the UCLA proposal is unnecessarily ambitious, and it sees no problem in beginning the selection process with presumed high (or low) exposure military units. Further, there are advantages to focusing on particular time periods when (a) spraying was heaviest and (b) the level of contamination of the herbicides with dioxin was highest. At a minimum, though, the procedure should be such that:

- for each man entered into the study his exposure must be assessed throughout his tour of service in Vietnam
- for each man entered, an exposure index, of the form proposed by UCLA, should be calculated
- at some point, individuals must be selected in random subsamples after the high and low exposure units have been identified (see point 5).

4. <u>The number of cohorts to be studied</u>

It is currently proposed -- both in the UCLA protocol and in the VA pilot study plans -- to select only two Vietnam cohorts, one with the highest ascertainable exposures and one with the lowest.

Since the assessment of exposure is so critical to the interpretation of the study results, the Subcommittee suggests that the design provide an opportunity to look for dose-response effects. The Subcommittee therefore suggests that three exposure groups be selected covering the entire range of exposure assessments -- low, medium, and high. By having the entire range of exposures represented, one would be able to utilize the exposure index of each subject in more efficient regression-type analyses, if they should be indicated, as well as looking for trends among the three exposure groups. This recommendation assumes that, as proposed by the UCLA protocol, an individual "exposure index" will be available and can be used for the definition of the three exposure groups. If, on the other hand, exposure indices are not calculated for each proposed member of a study cohort, then only presumptively high and low exposure cohorts will be identifiable.

5. Selection of the cohorts in sub-samples

The protocol's discussions of sample size are based on assumptions that the distribution of variables to be examined is binomial. Statistical estimates of power and/or sample size requirements in a study with so many outcomes to be evaluated actually have little sway in determining the actual size of the cohorts to be examined. However, some knowledge of the nature of the underlying distributions is necessary for the application and interpretation of significance tests -- the distributions cannot arbitrarily be assumed to be binomial. The Subcommittee suggests that the cohorts be selected as several independent samples -- say four. This would permit an assessment of the validity of the binomial assumption and provide a basis for a proper statistical analysis.

Further, if each of the high and low exposure cohorts are selected as a group of independent subsamples, there will be opportunity to compare the variability within each cohort with the variability between cohorts. This will enable discrimination between effects which result from the exposure to herbicides from other differences which may exist among companies similarly exposed to herbicides but having different exposures to other potentially harmful influences. The selection suggested here could be accomplished by randomly assigning candidate companies to one or another of the subcohorts before examining the individual records.

6. Forces to be included

The principal source of subjects for the study will be Army enlisted ground troops. The Subcommittee was asked for opinions regarding inclusion of some other groups. These opinions are as follows:

(a) Inclusion of Marines would be desirable if they can be included in sufficient numbers for separate analysis (e.g. 1,000-2,000 in each cohort -- this will probably require over-sampling) and if they can be included in each cohort in equal proportions to the total numbers of the cohorts. The latter is essential because of the likelihood of differences between Marines and other troops in entrance physical and other selective factors.

(b) Air Force personnel should not be included since they would unnecessarily complicate the analysis (if account were to be taken of between-service differences) and their principal exposed group (members of the Ranch Hand operation) are the subjects of an independent study now in progress.

(c) Officers, while offering the potential for being a highly exposed group because of multiple tours of service, should not be included since they can probably not be included in sufficient numbers for separate analysis. Further, the fact that many will have had multiple tours of duty in Vietnam complicates the assessment of their exposure and makes it unlikely that they can be included in equal proportions in the high and low exposure cohorts.

(d) Similar considerations as those described for officers apply to enlisted men with multiple tours of Vietnam duty. Any attempt to include them would greatly complicate the process of assuring equal representation in the several exposure cohorts. Further, the logistics of ascertaining their total exposure over multiple tours of duty becomes particularly complex when, as is proposed by DOD, the selection begins with exposed and not-exposed military units, rather than individuals.

(e) An important group to include if they can be identified are the crews and servicemen of Army-based helicopters used for spraying operations. They appear to have been among the most heavily exposed groups of all. Comparable non-exposed (or at least low exposure) groups could be assembled from the crews and servicemen of helicopter gun-ships and other helicopter operations.

7. Examination of mortality data

The UCLA protocol, and so far as is apparent the current VA plans, emphasize strongly the information to be obtained at the time

of questioning and physical examination of the selected cohorts. Only in correspondence subsequent to submission of the protocol do the UCLA investigators express any concern for the evaluation of mortality in the selected cohorts between the time of Vietnam service and the present. In the Subcommittee's view, the observation of cause-specific mortality in the selected cohorts both up to the present time and even more importantly into the future deserves much greater prominence than it has received. First, mortality data will provide the most objective and unassailable evidence for the presence or absence of some -- though certainly not all -- of the possible hazards of exposure. Second, mortality data up to the present may provide a basis on which to sharpen the questionnaires and physical examinations. For example, any excess of mortality from atherosclerotic heart disease among highly exposed individuals would have an important impact on the information to be sought at physical examination. Last, in comparison to the expense of the physical examination program, the mortality data can be assembled at very small cost.

8. Scope of the questionnaire and physical examination

The questionnaire and physical examination protocol included with the UCLA proposal are notable for their comprehensiveness. Indeed, they are formidable. While recognizing that this study is essentially a "fishing expedition", the Subcommittee believes that a questionnaire and physical examination protocol that are more focused and selective would lead to more enthusiastic participation and enhance the quality of information obtained. The Subcommittee believes that considerable revision of the current questionnaire and clinical protocol is required and offers the following recommendations:

(a) The protocols should be coordinated with those for the Ranch Hand study. The UCLA protocols are said intentionally to rely heavily on the proposed study of AO exposure among Australian troops in Vietnam. The rationale is to permit comparison of findings and mutual testing of hypotheses arising from either set of data. With the uncertainty regarding the future of the Australian study, it seems more important that the VA protocols be compatible with those of the Ranch Hand study. Further, the protocols for the Ranch Hand study have been carefully designed and tested and -- while the VA study may not incorporate all their components -- there is much to be learned from them.

(b) The pilot study for the VA study should not be implemented until findings from the Ranch Hand study are available. The guidance from that investigation should have a significant impact on the direction, methods and procedures of the UCLA project. Identification of key issues, organization of data collection including questionnaires and examinations such as special neurological and psychological tests, laboratory tests, etc. Ranch Hand may help identify areas where differences between "exposed" and "non-exposed" are most unlikely, borderline, or more dramatic. On the basis of the variability in the results in these three groups it should be possible to focus and expand on key outcomes and to eliminate some other areas of inquiry. The loss of time involved in waiting for these results should be more than made up through refinements in method and increased focus on key end results.

If a pilot study were undertaken prior to the availability of Ranch Hand results, and any substantial modification of the clinical protocols were subsequently required, the VA might find itself in the position of having to do a second pilot study. It is even possible that, if findings from the Ranch Hand study point to the possibility of a limited number of specific outcomes being associated with AO exposure, the cohort approach could be abandoned and replaced by one or more targeted case-control studies.

(c) While not quite so critical as the Ranch Hand morbidity results it is also conceivable, as noted elsewhere, that mortality data will be useful in modifying the clinical protocols.

(d) The present questionnaire needs especial attention. It consists of questions about health and non-health characteristics of the veteran and spouse and may be broadly described as covering demographic, lifestyle, and occupational items. Language varies from the vernacular which may be misunderstood in some groups of veterans to esoteric diagnoses which few will understand. Information on infections and parasitic diseases is skimpy and that on trauma and its consequences seems underemphasized. Opportunities should be provided in the pilot study for the participants for open-ended insertions -- particularly insertions of chemical, biological, and psychological exposures both in and out of Vietnam for which the participant may volunteer information. The emphasis on diagnoses rather than symptoms is difficult to understand,

since the questions (i.e. the terms) may be often misunderstood. A survey of symptoms present and past might provide more valid results -- and trigger in-depth probes to diagnoses regarded as key end points. The neurology questions require further evaluation -- the input of a neurologist experienced in this mode of inquiry would be helpful. A comparison of recent and past skills to uncover defects in coordination and equilibrium, sensation, muscle strength, intellect, speech, memory, etc. would be desirable. The format and topics of inquiry about pregnancies appeared better organized and more likely to uncover pregnancy wastage, perinatal death, malformations, mental retardation, etc. in the Ranch Hand forms than in the UCLA questionnaire. Specific questions for each pregnancy -- smoking, alcohol, use of drugs known or suspected of being teratogenic, should be determined and documented through medical records when feasible.

(e) The protocols should be focused, if possible, on known effects on humans and animals of exposure to phenoxy herbicides contaminated with TCDD. These would include effects on skin, reproductive organs, immune system, peripheral nervous system and liver function (including porphyrin metabolism).

(f) To satisfy scientific as well as political needs, the Subcommittee suggests a tiered approach to clinical testing. That is, a core battery of tests to be carried out on each subject with more sophisticated tests carried out on say 10-20 percent of the cohort. For example,

liver function (including tests for cholesterol and triglycerides), an immunotoxicity screen and a complete blood cell workup should be carried out on all subjects. Nerve conduction tests and sperm abnormality tests could be done on 10-20 percent of the cohort or as dictated by the answers from the questionnaires.

9. Quality control in the physical examinations

On the critical issue of quality control of data from clinical and laboratory examinations conducted in multiple sites across the nation, the UCLA protocol is silent. The issues will have to be addressed in much greater detail than is possible here. There must be a balance of high, medium, and low exposure cohorts at each examination site and during the course of the examinations. Inter- and intra-site differences will need to be assessed for each clinical characteristic examined and for all laboratory tests that cannot be centralized.

The Subcommittee recommends that these issues be begun to be addressed in the pilot study. There should be at least three examination sites in the pilot study so that variability in examination and reporting can be assessed. Further, these sites should not be the "best" or most cooperative sites that can be found under the exigencies of the current time schedule but should be selected so as to be more or less representative of the types of facility that are likely to participate in the main study.

10. Incentives

The Subcommittee was asked for an opinion regarding the use of incentive payments to reimburse participants for time spent in participating in the clinical studies. This time can be substantial -- approximately four days in the Ranch Hand study -- and it seems only reasonable that the participants would expect some compensation for it. The likelihood that an individual participant will benefit medically from his participation is small. It is likely that the incentive offered to the Ranch Hand participants ($100/day) contributes to the very high participation rate, and such an incentive is also likely to increase participation in the VA study. While it is true that the payment of incentives may bias the participation in favor of those who, for a variety of reasons, need the money, such bias will not be a source of real criticism if a participation rate approaching that of the Ranch Hand study is obtained. Even if it is not, the bias should in considerable degree apply similarly to the different exposure cohorts. On balance, the Subcommittee believes that to offer an incentive is an appropriate thing to do.

11. Responsibility for the main study

The question has been raised as to whether the VA should itself accept responsibility for coordinating the main study or whether this task should be contracted out. VA hospitals have some of the best clinical and laboratory facilities in the country, and many have considerable experience of participation in multi-site studies. The desirability of using these resources should be assessed when the perceptions and attitudes of veterans towards examinations in VA facilities have been determined (see point 13).

However, the Subcommittee believes that a stronger central scientific team to coordinate the whole effort can be assembled outside the VA than within it. Location of ultimate responsibility outside the VA would have the additional political advantage of making it quite apparent that the VA, on its own or under pressure from any of its many constituents, could not in any way influence or conceal the findings. The Medical Follow-up Agency of the National Research Council would, for several reasons, not be an appropriate organization to coordinate this study. The Subcommittee recommends that the study be conducted by some university group that is strong in epidemiology and biostatistics and has experience in national collaborative studies. The model followed in many cooperative clinical trials, in which a Coordinating Center which conducts the day-to-day business of the study and is responsible to a Steering Committee representing each of the participating clinical units, would seem to be a suitable one here.

If this option is chosen, the Coordinating Center should be selected first and should have input into the selection of the participating clinical centers.

12. Confidentiality of the questionnaire and clinical protocol

The VA has gone to considerable lengths to maintain the confidentiality of the proposed questionnaire and clinical protocol. The rationale has been that if such material became public there would be opportunities for participants to be coached into responses that some groups wish to see. The Subcommittee believes that (a) the opportunity for such coaching exists whether or not the specific details of the questionnaire are known, (b) there is no evidence

that such coaching is actually intended by any group, (c) as other reviewers have pointed out, the important thing from the point of view of questionnaire validity is to ensure that the respondents are unaware of the exposure cohort to which they are assigned -- in which case inaccurate or deliberately false responses should not introduce associations that do not in reality exist, and (d) the policy runs the risk of alienating individual veterans and veterans' organizations whose collaboration will help assure the successful completion of the study. The Subcommittee recommends that copies of the present protocols and of subsequent modifications of them be made available to interested parties.

13. Representation of the socio-behavioral sciences

The Subcommittee notes the almost total lack of input from the socio-behavioral sciences in the present protocol. Representation from these fields would strengthen the questionnaire and other aspects of the study design. In addition, the cooperation of veterans -- both as organizations and as individuals -- is essential to the success of the study. Behavioral scientists should determine how the study is perceived by individual veterans at each step of the protocol. If the study population becomes disenchanted with the conduct of the study, the study may fail or its results may fail to convince those who need to be convinced.

14. Financing of the study

In providing for this program to go forward, the VA's highly productive medical research program must be protected; funds for the Agent Orange study should be supplied separately and not diverted from the VA medical research funding.