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ADVISORY COMMITTEE:
CRITIQUE OF THE RANCH HAND MORBIDITY DRAFT REPORT

On February 6, 1984, a meeting of the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants was held at NIH, 9:30 AM - 4:30 PM, to discuss the draft report on morbidity among Ranch Hand (RH) personnel. The list of Air Force scientists in attendance is attached. The Advisory Committee, convened on short notice, was present except for Dr. Selikoff, who had developed the flu, and Dr. Comstock, who was able to attend only in the afternoon. Dr. Gilbert W. Beebe, a biostatistician with long experience in studying the health of military veterans at the National Academy of Sciences, served as a consultant throughout the day.

Four Air Force scientists presented a thirty-minute summary of their results. Each Committee member was asked to suggest topics of special importance to the discussion from his point of view.

Our advice concerned a) modifications of the present interim report and b) development of additional information for future reports -- intermingled at the meeting, but here presented separately.

A. FOR THE INTERIM REPORT:

1. Add more a priori structure to the report by describing hypotheses to be tested concerning the occurrence of chloracne, soft tissue sarcoma, porphyria cutanea tarda, psychological or neurologic effects, immunologic perturbation, and genetically induced impairment of reproductive performance. Give the background for each possible effect at the outset, and return in the Discussion to the hypotheses.
2. Describe in the Executive Summary (ES), text and conclusions the elements that help establish causality, and weigh each of the findings in this regard (i.e., the presence or absence of a dose-response effect, biologic plausibility, consideration of explanations other than herbicide exposure, the correct temporal relationship (exposure before onset of the disease), the specificity of the association and the consistency of the findings). Indicate how each finding measures up. The excess of skin cancer, for example, did not exhibit a dose-response effect. Among the flying enlisted personnel the response was in the wrong direction: it was greatest among those who were the least exposed.
3. Do not summarize the number of comparisons for which probability (p) values indicating that differences between the groups were unlikely to be due to chance. Psychologic test-scores in particular are not independent of one another and add disproportionately to the number of differences between the groups compared. These differences may have antedated the experience in Viet Nam or have been due to influences other than exposures to herbicides. Also, some differences favorable to the RH group have been added to those that are unfavorable, and p values for unverified subjective information have been given equal weight to those for well-documented objective observations.

4. Known (and unknown) effects from smoking, alcohol and diabetes were easily detected in this study, in contrast to the findings with regard to effects of herbicide exposures. This contrast should be featured in the ES and the text.
5. Further description of the intensity and nature of the exposures, as well as their known effects, would enhance the reader's understanding; i.e., 2,4-D, 2,4,5-T, dioxin, malathion, arsenic -- and the possibility of as yet unknown contaminants. How much of each was used, and who was most heavily exposed, on the ground or in the air?
6. The absence of chloracne thus far needs special attention. Can other effects occur without a history of chloracne?
7. Describe the etiologic possibilities other than herbicides for the decrease observed in peripheral pulses in the RH group vs. the comparison group. Do the same for skin cancer, transitional cell carcinoma of the urinary bladder, reproductive outcome, psychological test-scores, and learning disabilities among children as described in the interviews with their parents.
8. Mention the possibility that the elevated levels of thyroid hormones in the blood of the RH group suggests that, in accord with animal experimentation, the effects of dioxin may be mediated by the thyroid.
9. Describe the differences between genetic effects conveyed by germ-cell mutations in the sperm as contrasted with teratogenesis in which malformations, an effect on the embryo, occur because of maternal exposures during pregnancy (not possible in this study).
10. A germ-cell mutation should induce a known genetic disease, not an ill-defined assortment of defects, such as skin blemishes.
11. The point should be made that comparison groups are likely to differ from the RH group in characteristics or exposures before, during and/or after military service. The best one can do is to come as close as possible to selecting a comparison group that differs minimally from the cases except for herbicide exposure. The possibility should be constantly in mind that differences other than herbicide exposure, e.g., media attention, may influence the results.
12. Add the findings on sperm to the Executive Summary.
13. Rephrase the statement, "This baseline report is not negative."
14. Delete Table X-5 because it combines etiologically dissimilar cancers (of the genitourinary tract) and replace it with Appendix X, which is far more informative because it lists diagnoses histologically in a way that can be etiologically meaningful. The occurrence of three cases of transitional cell carcinoma of the bladder should be explained.

15. Reports of miscarriages are notoriously inaccurate and should be regarded with great caution.
16. The word "overselected" is inappropriate in describing the selection of the 18% who did not fit the criteria for the comparison group.
17. The statements that certain findings are "of concern" should be modified because what is really meant is that they merit further study. None has been causally related to herbicide exposure.

B. IN THE FUTURE:

- 1) Review promptly the military medical records for acute illnesses at the time of herbicide exposure, looking especially for the known effects of the various agents used.
- 2) Give the age-distribution of the men with skin cancer. Each case should be briefly described. A case-control study might reveal factors that contributed to the occurrence of these neoplasms.
- 3) With regard to the men with urinary bladder cancer, give the case-histories including exposures to known carcinogens.
- 4) Consider a case-control study of the RH men with diminished peripheral pulses. Could this finding be due to a "jack-hammer" effect from the aircraft they used?
- 5) The data on the children are from hearsay only, and may be heavily influenced by differential reporting. Confirmation by review of medical or school records may be possible. The plausibility of the genetic origins of any differences found should be evaluated.
- 6) Data on stillbirths and neonatal deaths should be confirmed from medical records, and combined.
- 7) A separate report should be published on previously unknown physiologic effects of smoking and alcohol use as found in this multiphasic study.

Overall, we advised that the Executive Summary be expanded, that emphasis be placed in it and elsewhere on the elements necessary in establishing causality (not just p values) and how the findings meet these criteria. Modifications of the text were advised but no further data analyses were needed for this report. Several by-product studies appeared to be worthy of further development, especially in relation to previously unknown physiologic effects of smoking, drinking and diabetes, as studied epidemiologically.

Robert W. Miller, M.D.

MINUTES, AGENT ORANGE MEETING

Robert W. Miller, M.D.

On February 6, a meeting of the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants was held at NIH to discuss the draft report on morbidity on Ranch Hand personnel. Four Air Force scientists led off with succinct summaries of the findings. Each Advisory Committee member was asked to list topics of special importance to the discussion from his point of view. The report was judged to be clearly written and well-organized.

Exposure: The text can be clarified concerning the diversity of exposures: 2,4-D; 2,4,5-T; dioxin, arsenic, malathion, and/or other unknown contaminants. The discussion brought out the nature of the heavy exposures of some ground personnel in a way that the reader cannot derive from the report as it is presently written. This information should be added. Mention should also be made of the absence, as yet, of anecdotal accounts or data from clinical records on acute medical effects from the exposures, in contrast, for example, to Japanese mustard-gas workers who suffered acutely from chemical effects on the skin and respiratory tract. This information should appear in the text and in the Executive Summary (ES). It was noted that the data had not been analyzed as to the number of missions flown because this information was not well recorded for enlisted personnel. It should be made clear that effects of exposure on health might be due to any one or a combination of the chemicals to which Ranch Hand personnel were exposed.

Hypotheses: At the outset of the report, known effects of various exposures, experimentally and/or in man, should be described — not just for dioxin. (Example: Arsenic may induce skin or respiratory cancers.) In general, the study should focus on hypotheses based on information from previous studies. In the Discussion, the authors should return to these hypotheses in evaluating the results. More a priori structure to the study and interpretation of the results would enhance the presentation. The other abnormalities found, then, are incidental and problematic.

The elements in establishing causality should briefly be described in the text and in the ES. They are crucial to understanding the observations made. They are: 1) a dose-response (strength of association); 2) consistency of the association; 3) temporally correct relationship; i.e., the event must precede the disease; 4) specificity of association; 5) biologic plausibility; and 6) consideration of possible explanations other than herbicide exposure.

One reviewer with long experience in the research use of military medical records was surprised that the review was not yet complete for illnesses at the time of the exposure.

Chloracne: No cases of chloracne are known among the Ranch Hand group. Discussion of this observation would be helpful. Can one have other

effects of dioxin without having chloracne? Some investigators claim that without chloracne, a search for other effects is not warranted. It was pointed out that mice are relatively insensitive to chloracne but develop other effects from exposure to dioxin. In the Missouri horse-arenas contaminated with dioxin, one of two children who played in the dirt containing dioxin developed hemorrhagic cystitis but not chloracne. Exposure at the same site killed about sixty horses and numerous birds. Other components of the herbicides are not known to cause chloracne. Each of the above items should be mentioned in the ES.

Abnormal Pulses: Pulses at five anatomic locations showed a statistically significant decrease in the RH group. The reason is unknown. RH flying personnel experienced vibrations in their aircraft, unlike that of the comparison group, we were told. The possibility of a "jackhammer" effect on the vasculature was raised, as is known to occur in workers who use these devices. Certain drugs or chemicals; e.g., ergot, might also narrow the lumens of blood vessels. For this and other unexpected findings described in the report, case-control studies might reveal contributing factors, inborn or due to environmental exposures, not necessarily herbicides. In this way the study might yield extra dividends of information.

Skin Cancer: The absence of a dose-response effect suggests that the excess of skin cancer is due to herbicide exposure. The age-distribution of the men with skin cancer should be given, and a case-control study made to seek possible causes. For all such findings, a brief description of the history of the illness and physical findings should be given. Adjustments have not yet been made for sun exposures according to place of residence.

Genitourinary Cancer: This category of neoplasia is terribly mixed with regard to etiology (prostate cancer vs. testicular cancer vs. bladder cancer vs. kidney cancer). The lack of a difference from the comparison group is shown in Appendix X, which should be substituted for Table X-5 in the text. At first glance, Appendix X raises suspicion about the occurrence of transitional cell carcinoma of the urinary bladder among young men exposed to herbicides, but one of the three developed his neoplasm at the time of exposure; that is, without a latent period. The other two cases occurred after a long-enough interval, but are too few for drawing inferences about the role of herbicide exposure. These two cases should be evaluated with regard to exposure to other known bladder carcinogens (most such cancers are environmentally induced). Appendix X should be labeled "Cancers, Excluding Skin."

(NOTE: Suggestions that involve recontacting the men or their families are for future studies and not for inclusion in this report. No further analyses of data were suggested before issuing this report.)

Reproductive Outcomes: The excess of birth defects among children of the RH is due to miscellaneous skin blemishes at birth. One would expect mutation to cause a known genetic disorder, such as chromosomal abnormalities or xeroderma pigmentosum. The birth defects were ascertained by history, not by examination of the children. Their birth records have not yet been reviewed. Unequal reporting by the parents in the groups

compared may be involved here. The specific diagnoses of the skin abnormalities should be ascertained and listed in a future report.

The text for the present report should emphasize the distinction between genetic effects transmitted through sperm, and teratogenesis, which occurs due to exposure of the embryo early in pregnancy. None of these children were exposed in utero. Therefore, the skin blemishes observed cannot be due to a teratogenic effect of herbicides.

Reports by parents of miscarriages are notoriously inaccurate. Stillbirths and neonatal deaths are more reliable, can be verified, and may be combined.

The most solid observation is a lack of a difference between the groups in the morphologic observations of sperm. This finding, omitted from the ES, should be included in it.

Learning Disabilities: Again, because the data on learning disabilities among children are entirely from interviews with their parents, the responses are highly subjective. Differences in reporting or in parental attitudes toward the children can influence the results. If parents were concerned about the fathers' herbicide exposures, they may be anxious about the health of their children. Overprotection, for example, can lead to the "vulnerable child syndrome," as in youngsters with heart murmurs in infancy who are later found not to have disease, and the murmurs disappear spontaneously. Continuing parental concern, though, can affect the behavior of the children.

Hyperthyroxemia: The statistically significant higher levels of certain thyroid hormones in the blood of the RH group were of great interest pharmacologically, for the observation raises the possibility that dioxin disrupts the function of the thyroid. Studies of experimental animals have shown that the thyroid mediates the effects of dioxin.

P Values and Psychological Test-Scores: The listing of the test-results in Appendix XVIII and some statements in the text and Executive Summary (ES) indicate that the RH group differed significantly from the comparison group far more often than one would expect by chance. The report does not make clear that in some instances the RH group had more favorable test-results, and that a substantial proportion of the "adverse" differences were in the numerous components of the psychological test-scores. These values are not independent of one another, so the same attribute can influence various test-scores. The psychological attributes may have been present before the men entered the Air Force, or the attributes may be due to the experience but not related to herbicide exposure. One would have to postulate an interaction between exposure and educational level to explain why high-school graduates showed an effect and college graduates did not.

Effects of Smoking, Drinking, Diabetes and Age: The study clearly shows the known effects of these variables, as well as physiologic effects not previously known -- in particular, the effects on immunologic function. These new findings will be separately reported and seem to be an important

by-product, which may open new avenues of research. The capacity of the study to reveal these effects should be described in the ES, perhaps in comparison with the results as they relate to herbicide exposure.

The Groups Compared: In this sort of study the groups compared should be alike except for herbicide exposure. Because self-selection and military assignments differ according to the work involved, it is probably impossible to select groups for comparison that do not differ before the assignment. In epidemiologic research one must take things as they are, rather than as they might ideally be (e.g., the ideal might be identical twins reared together, one assigned to RH and the other to the comparison group). The Air Force investigators selected a reasonable comparison group, as was confirmed by four independent peer review committees. The data on duty assignments of the comparison group were recorded in a fashion that misclassified some men. After the study began, it was found that 18% had not served in Southeast Asia, as was required by the study protocol. The comparison group consists of a) those who matched the cases and agreed to be examined, b) those who declined, c) those who replaced the men who declined, and d) the ineligible 18%. The Air Force research group has grappled with the question of the best means to avoid biased results in analyses that make use of the original comparison group with or without the replacement group or the ineligible group. The Advisory Committee did not go into this question and did not disagree with the handling of the data analysis for this report. Future analyses can evaluate the differences in results when comparison is made of available data for each of the groups that participated, as well as the incomplete information available for those who did not. Such studies may be interesting to an epidemiological audience, but the biologic implications of the results to date concerning exposures to herbicides are unlikely to be altered. The word "overselected" was deemed inappropriate for describing the erroneous selection of men who were ineligible for the comparison group.

The Advisory Committee strongly urged modifying the statement "this baseline report is not negative" to one that stated that no effects attributable to herbicide exposures have as yet been detected. This conclusion does not exclude the possibility of undetected effects or effects which may not yet have occurred. The Committee viewed the findings "of concern," to be findings in need of further exploration. None appeared to be causally related to herbicide exposure as indicated by the lack of a dose-response effect, biologic implausibility, and/or alternative explanations for the effect in question.

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