MINUTES RANCH HAND ADVISORY COMMITTEE MEETING
October 14-15, 1999

Parklawn Building, Conference Room K
Rockville, Maryland

The meeting was called to order by chairperson Dr. Robert W. Harrison at 8:30 a.m., Thursday, October 14, 1999. Other committee members present were: Dr. Turner Camp, Dr. Irene Check, Dr. Delores Shockley, Dr. Michael Stoto, and Dr. Robert Trewyn; Consultants and staff present were: Dr. Robert Delongchamp, NCTR, Consultant; Dr. Sonia Tabacova, NCTR, Consultant; COL Harry E. Marden, M.D., Consultant; LTC Julie Robinson and LTC Bruce Burnham, former and present Chief of Population Research (Brooks AFB), Dr. Joel Michalek, Principal Investigator (Brooks AFB); Mr. Ronald Coene, Committee Executive Secretary; Ms. Barbara Jewell, NCTR, Committee Staff. For the Army Chemical Corps Study on presented on October 15th: Dr. Rebecca Klemm, Dr. Mary Paxton, Dr. Han Kang (VA), Mr. John Boyle, Dr. Nancy Dalager, and Dr. Carol Magee.

Observers were: Dr. George Claxton, VVA; Dr. Weihsueh Chiu, GAO; Maurice Owens, SAIC, Program Manager; Dr. Jay Miner, Program Management Support; Manuel Blanca, Program Management Support; Meghan Yeager, SAIC; Dr. William Grubbs, SAIC; Peter Mazzella, DHHS; Otto Kreisher, Copley News Service; Dr. Linda Schwartz, Vietnam Veterans of America.

OPEN COMMITTEE DISCUSSION

Dr. Harrison opened the meeting and welcomed the committee members, with a special welcome to Dr. Favata, who was not able to attend the last meeting in person. Dr. Stoto was unable to attend the morning session this first day.

The *Minutes* of the August 26-27, 1999 meeting were discussed and, with no substantive changes brought up by the committee, were approved by a voice vote.

Mr. Coene referred the committee to its discussion about the availability of the draft Air Force report to the public at the August meeting. He informed members that this document falls into an exemption under the Freedom of Information Act which says that the government can maintain the confidentiality of information if it is considered predecisional. He said that accordingly, nothing would be released today.

Old Business was moved to after lunch so Dr. Stoto could participate in the discussion.

REVIEW OF THE AIR FORCE HEALTH STUDY CYCLE 5 DRAFT CHAPTERS

Chapter 11 - Neurology. The reviewers of this chapter are Drs. Favata and Shockley; Dr. Michalek made the presentation. In it, he summarized findings that appeared statistically significant. He discussed an increase in inflammatory diseases, but said that result had little real statistical meaning. He said the data showed a significant increase in the index of polyneuropathy when comparing moderate versus mild or none on all Ranch Handers and in the high category and against current dioxin. Another run through the data showed it correlated significantly with dioxin.

Dr. Favata thought that the dependent variables were appropriate and comprehensive, and commented that the range of motion of the neck has no significance in testing the 11th cranial nerve. She asked why the cranial

nerve index excluded the spinal accessory nerve; Dr. Grubbs responded that this analysis has been done this way since 1985.

Regarding deep tendon reflex coding, Dr. Favata said she disagreed with the designation of sluggish or very active reflexes as normal, preferring to see the traditional graded designation of 1+ equals sluggish, 2-3+ normal, 4-5+ very active. Dr. Michalek asked her if she would like to see what is called an ordinal categorical analysis rather than a simple binary analysis, and she said yes.

Dr. Favata stated that the covariates chosen were appropriate and comprehensive, and that in further evaluations the study report should include repetitive motion exposure.

Dr. Shockley told Dr. Michalek that his oral presentation was clearer about the significance of an association with inflammatory diseases than the written draft. He said he would review the draft.

Dr. Harrison questioned the Air Force about the assessment of neck range of motion, saying it was apparently very subjective. Dr. Michalek remarked that the meaning is not apparent. he then questioned the idea that neurological abnormalities were related to the diagnosis of diabetes. Dr. Michalek said that was in the article, but not in this report. He said they computed the relative risk of peripheral neuropathy against diabetic status; not the World Health Organization or American Diabetes Association status. Also, the study does not relate the known length of the diabetes to the occurrence of the neurological complication. Dr. Harrison said he thought that dioxin levels and obesity were related. Dr. Michalek stated that the analyses were adjusted for body fat.

Dr. Michalek then went through how the diabetes definition used by the study was developed with help from NAS. He said that diabetics were in the analysis, but with a covariate for the presence or absence of diabetes. Dr. Harrison said he was interested in whether or not further analysis had been done to show that it made sense in terms of length of disease. Dr. Michalek said that had not been pursued. He said the relation between diabetes and peripheral neuropathy was very strong in both controls and Ranch Handers, and in all physical exams.

Dr. Camp asked if the study showed a causal relationship between diabetes and obesity; Dr. Michalek said they didn't know, and could only study associations. Dr. Harrison told Dr. Camp that it has been clinically observed that patients with Type II diabetes tend to gain weight the longer they live. And also, that if you took away obesity, 60 percent of Type II diabetes wouldn't exist; indicating that obesity is a strong contributor to diabetes. He further observed that diabetes and hyperlipidemia are associated. Dr. Harrison said the study report should not use the term insulin-dependent, because that term is reserved exclusively for Type I diabetes. Type II diabetics on insulin are termed insulin-requiring.

Chapter 14 - Cardiovascular. This chapter was reviewed by Drs. Trewyn and Tabacova, and was presented by Dr. Michalek. He reported that many findings are negative in this chapter.

Dr. Michalek told the committee that one strong association is the enlisted ground crew, which had the heaviest exposures, experienced significant increases in cardiovascular mortality.

Dr. Trewyn told the group that the cardiovascular assessment focuses inordinately on dioxin rather than herbicides. Also, he said, there seemed to be a lot of jumping back and forth in the summary and the conclusion between what's significant and what's nonsignificant, and did not help him understand the data that's in the chapter.

Dr. Trewyn asked if the data from the '94 Air Force mortality update was not included; and thought that it would help, because one can then discuss the relevance of those numbers of the people who have died, and it would

help round out the information in the chapter.

Dr. Camp stated that reputable people do see a connection between diabetes and heart disease. Dr. Michalek said that very few of those men that died of heart disease would have come to the study's physicals; and the only avenue is researching medical records, a lengthy process. Dr. Harrison said he felt Dr. Camp's statement should be worked on.

Dr. Tabacova felt the study was well done and comprehensive. She questioned how current alcohol and cigarette smoking data were used with which dependent variables. And, dioxin has been adopted in the study as an exposure measure for pesticide exposure, she is interested in seeing an analysis of how this exposure measure relates to the outcome.

Dr. Grubbs replied that current alcohol and current smoking were used in everything else but the historical variables.

Dr. Michalek informed the group that the study has done analyses of dioxin versus health in the control group, and that will be published soon in *Epidemiology*.

Dr. Harrison inquired further about deaths from heart disease in the study group. Dr. Michalek stated that many of the cardiovascular deaths occurred before the study started.

Dr. Favata asked about the possibility for autopsy release and further study of organs. Dr. Michalek stated that they always make efforts to obtain them. Dr. Miner said the effort to obtain records is made with every subject. Dr. Favata also inquired about tissue analysis, and was told that efforts are always made to obtain specimens; but the results are very sparse. Dr. Michalek said the number of autopsies done was very disappointing, also. Dr. Camp added that the VFW makes efforts to get the families to allow autopsies, because is often supports a veteran's claim.

Dr. Check observed that no protocol exists for autopsy, and others felt that one should be developed. Dr. Michalek stated that the study has one, developed by CDC, and discussed the difficulties in getting it put to use. He said that so far there have been 118 Ranch Hand deaths and about half of those occurred before the first physical. He stated that "overall, there is nothing going on with mortality. It's only when you look in the subgroups by cause that you see the big increase, or the significant increase in heart disease deaths in the enlisted ground."

Dr. Delongchamp said that the way the report has analyzed its data is with methods that look at prevalence, and they don't really deal with competing risks very well or anything like this, which is what this whole mortality issue raises. He said that if you wanted to evaluate neoplasia and cardiovascular disease, you would want to look at deaths, and that data is not in the report. In talking about doing cohort studies, different analyses are required.

Dr. Michalek stated that this has happened already in articles. Any analysis that would incorporate mortality would have to be Model 1, which is just all Ranch Hands versus all Control, adjusted for occupation. He said, "We have a proposal to address exactly that point in the next report, which will include mortality and morbidity in the final report, and include all prevalence; not just the ones that showed up at the clinic this time, but the ones that showed up in previous cycles, too, and all morbidity." He said current reports are snapshots.

Then there was a general discussion about the changing mixture of subjects showing up for the exams over the years, as they age.

Chapter 10 - Neoplasia. This chapter was reviewed by Drs. Check and Camp, and was presented by Dr. Michalek. He reported that the findings here were generally negative and internally inconsistent.

Dr. Michalek said the Ranch Handers were having less than the expected number of cancer deaths as a group, and no evidence of increased cancer deaths in the enlisted ground crew.

Dr. Check agreed with the observation that there are a lot of internal inconsistencies in the data, but chose not to address it. She prepared printed copies of her summary, and tables. Skin neoplasms were considered separately from the systemic neoplasms. Dr. Check prepared two summary tables of this data. She felt it important to know whether any of those benign neoplasms might be considered to be premalignant lesions.

She discussed the data in detail, noting that the number of non-melanoma malignant neoplasms did not equal the sum of basal and squamous cancers. Dr. Grubbs explained that there are overlaps; people with a malignant and a benign. Dr. Check said that an explanation in the report would help, and then suggested the report say how many of the patients or subjects had more than one neoplasm.

Also, Dr. Check felt there should be a definition of the non-melanoma malignant. She also asked for an explanation of which category carcinomas in situ would fall into.

She noted that the data provided confidence that there is no association between dioxin and prostate cancer; but the lung cancer association needs to be discussed and examined further. She said it was not clear how the data from the mortality study are connected with this data. She expressed interest in the next study answering the question: "Does dioxin shorten latency time?"

Dr. Check said she was impressed with the comprehensiveness of the examinations and that the data are presented in an orderly, 'uninteresting' manner. She concurred with the authors' conclusion that there is no gross dioxin effect.

Dr. Camp observed that the Secretary of Veterans Affairs, the Institute of Medicine or others may accept an association or even a suggested relationship between dioxin exposure and the diseases being studied, and might recommend service connection.

Dr. Trewyn felt sections should not be titled "no significant difference" in incidence and prevalence of neoplastic disease. He discussed a study supporting the idea that some low dioxin effects may be more significant than a high dioxin effect, which Dr. Harrison expressed a desire to see a copy.

Dr. Harrison expressed concern that what the report is calling high dioxin is really high dioxin in a cell culture system.

Dr. Delongchamp then discussed cancer deaths in the study group with Dr. Michalek, stating that a reduction in prevalence could really be a sign of an increase in mortality. Dr. Michalek said that overall, they were having less than the expected number of cancer deaths. He echoed the frustration that the report doesn't take into account the mortality data along with the morbidity data. Dr. Delongchamp theorized that at higher doses, people were getting heart disease and dying; and at lower doses, they were getting cancer. Dr. Michalek replied, they already died of something else and therefore they didn't live long enough to get cancer, and so the rates are low in the high category. He stated that scenario comes up whenever they write reports, but there is no data to test the hypothesis.

Dr. Harrison asked about the rates of prostate cancer for black men in the study group. Dr. Michalek stated that the Ranch Handers were only 5-6 percent African-American, too small a number to study racial effects.

Dr. Delongchamp inquired about the study making any adjustment for birth cohort. Dr. Michalek referred him to the cancer article, recently published in the American Journal of Epidemiology. He said the paper does not suggest an exposure effect. Dr. Harrison inquired about an adjustment for fatness at exposure; which Dr. Michalek said was a covariate in Cycle 4. It was removed from the models.

OLD BUSINESS

Disposition of Health Study biological specimens.
Dr. Michalek started by saying he felt putting an RFP through the NIH was the most coherent idea. NIH was considered to have the capacity to review a multitude of anticipated proposals. Dr. Miner added that they charge a substantial overhead fee for doing that. The committee discussed the possible scope of work and what a "reasonable" amount of money would be for the contract.

Several places mentioned to consult at the NIH were: the National Institute of Environmental Sciences; NRRC, (the General Clinical Research Centers); and Cooperative Human Tissue Network (Roger Aamodt). Dr. Harris mentioned possible use of study sections that are not NIH-run that do evaluations for the Army health initiatives.

Dr. Michalek asked the committee to think about the specimens philosophically; to consider why these specimens were collected. Or, could they be used to answer a question like diabetes. Dr. Trewyn posed the question of timing of work contemplated in the RFP in relation to the study.

The committee felt that this should be communicated as a committee's recommendation to the Secretary. The proposal was put in the form of a motion, and was unanimously approved by a voice vote. Dr. Harrison said that the committee should consider doing that RFP before the next study start. Later in the discussion, he mentioned exploring the use of the Scripps CRC, where certain expenses would be covered under the umbrella of enhancing clinical research through collaborating with NIH.

Afternoon Session

Dr. Harrison spent a few minutes with Dr. Stoto, bringing him up to speed on what he missed in the morning session.

Discussion of the issue of Ranch Hands versus Comparisons
Dr. Trewyn expressed concerns about herbicide exposures being different because the types used in aerial and ground spraying are different; and that problems arose because the in-country versus out-of-country comparisons would have had different exposures; and that the chemicals sprayed would have been different.

Air Force Response to Questions from Last Meeting
Dr. Michalek said he had a set of slides to address comments raised at the last meeting. From the last meeting were: a Comparisons issue that Dr. Trewyn mentioned. What is the proper referent cohort? What about dioxin versus herbicides? An extensive discussion ensued. Dr. Michalek told Dr. Trewyn that the question can be answered based on the qualifying tour data only, or he can answer it based on flag Vietnam tours; but this has not been done yet. He gave the study definition of a control:

To be a control you had to be in a specified collection of C-130 units, and you had to be there in a certain window of time, between 1961 and 1971, and you had to be active duty Air Force. The data deals with multiple tours and variable tour lengths; some of those tours were years long, others were just 90-day TDYs, and they were all interspersed. Dr. Michalek presented a sample of the data in a series of slides.

Dr. Favata remarked that that isn't addressing the central question of the effect of herbicide exposure. By

noting their presence in Vietnam, that really didn't characterize their exposure appropriately.

Dr. Stoto discussed two possible studies here; one is a study of being in a Ranch Hand operation. The study is fundamentally a study of, what were the health effects of being in the Ranch Hand operation compared to other people who were like them in every respect, except they weren't in the Ranch Hand operation. He said we are inferring that anything that we find is due to the herbicides that were used in the Ranch Hand operation.

He told Dr. Michalek he thought the fundamental idea was to look at people who were in Vietnam compared to people who were not in Vietnam, regardless of their Ranch Hand status. Also, he pointed out, the other study that came up after the protocol was designed is the dioxin study, because it was discovered that you could measure dioxin. And now there was a separate study that looks at the relationship between health outcomes and dioxin as estimated based on the serum measurement.

Dr. Trewyn stated that yet another study idea is based on the hypothesis that herbicide exposure has caused adverse health effects in a portion of the Comparison group that could be removed from the study. Dr. Stoto disagreed with that, and Dr. Harrison opined that one group then should be exposed to phenoxy herbicides and the other group should not. Dr. Trewyn agreed, and Dr. Stoto stated that the groups also need to be as similar as possible in every other respect.

Dr. Stoto stated that the second hypothesis is one that evolved after the serum dioxin measurement became feasible.

Dr. Trewyn told the committee there were blue and white compounds, and those did not contain dioxin. He said he would "love to know for sure what was sprayed around the base camps." -- where exposure to anyone who served in Vietnam may have been different than the Ranch Handers per se.

At Dr. Miner's request, Dr. Michalek read the purpose of the study from the protocol. The purpose of the study, of this investigation is to determine whether long term health effects exist and can be attributed to occupational exposure to herbicide Orange. Later on, "herbicide Orange" is replaced simply with the word 'herbicides' in the protocol.

Dr. Schwartz remarked about nurses' use of Agent Orange to keep grass down around the hospitals and their living quarters. Dr. Harrison said he assumed that none of the Comparisons were in Vietnam, and that they were never in contact with Agent Orange. Dr. Trewyn said that was his assumption, also.

Dr. Stoto told the committee that epidemiology is full of compromises. "What you want is to get a trade-off between getting groups that are as different as possible on the main thing you're trying to study and as similar as possible on everything else." He said that to achieve the similarity requires careful matching, and that probably came at the expense of some degree of herbicide exposure among the controls. He said this probably doesn't compromise the main study object.

The committee discussed possible comparisons to study differences, were this nine percent of Comparisons that were in Vietnam removed from that group. Dr. Delongchamp asked whether what members are interested in is whether the p-value gets smaller by removing this group. Dr. Harrison replied that he was interested in whether the difference becomes more significant.

Dr. Miner and Dr. Stoto discussed the toxicity of white and blue herbicides. Dr. Harrison stated that this sounded like a tough issue to resolve. Dr. Michalek proposed that the committee think about it and exchange email to try to devise a meaningful analysis, and then talk about it later, reporting the results to Dr. Harrison.

Dr. Trewyn led the group into a discussion of the use of cut points when Scripps normal ranges were not

available. Dr. Michalek said he generally relied on textbook cut points or Scripps normal ranges, except in certain cases like luteinizing hormone where the study developed its own, better data.

Dr. Stoto and Dr. Harrison got engaged in a discussion about clinical significance versus the clinical significance versus statistical significance of the mean serum levels of free testosterone and total testosterone being slightly higher in Ranch Hands than in Comparisons.

Dr. Harrison and Dr. Michalek discussed the relationship between testosterone and luteinizing hormone. Dr. Michalek said they try to entertain any possible deviation from what is observed in the Comparison group without any condition applied, a priori. Dr. Harrison talked about the drawing of conclusions by comparing values, all of which exist well within the normal range, and either implying or actually stating that it suggests a difference between the two groups.

Dr. Stoto said concerning summary tables currently only giving the p-values and not absolute differences in the data, that for the half dozen or so things that are in Chapter 19 that look like they're important differences, that for those outcomes that they report not only the statistical significance but the actual measures, so readers can make a judgment about whether they think that's important.

Dr. Harrison said he thought the purpose was to figure out if any of this was causing a health effect.

Dr. Trewyn said he wanted to make sure that the numbers were there and that the potential for interpretation was there; that something wasn't being thrown out as being meaningless when perhaps it might have been. Dr. Michalek stated he felt confident that has not happened.

Dr. Michalek took up the question, What is the appropriate comparison group? He told the committee that all of this was argued out in 1978-1979 time period, in front of the National Academy of Sciences, Armed Forces Epidemiology Board, the Air Force Scientific Advisory Board and the UT School of Public Health, a scientific group that was used for peer review. So it ended up Vietnam veterans versus Vietnam veterans.

Dr. Michalek said if you want to wrap up the Agent Orange issue the best we can in our lifetime, probably the next five or ten years, an idea would be to reactivate the Vietnam Experience Study and bring the Army Chemical Corps study to conclusion, and bring the Ranch Hand Study to conclusion, and then summarize everything we've got.

Dr. Michalek presented data on the use of three herbicides in Vietnam, and the percentage of dioxin contamination varied. Dr. Camp said that from the claims standpoint, this was very important.

Dr. Michalek then addressed topics posed by Dr. Favata. It does happen that our study subjects get exposed right here in the United States to dioxins. One of our controls reported the same problem. The EPA has a database of counties in the United States, rank ordered by dioxin exposure. We also know the complete residential history of all of our veterans by zip code, by longitude-latitude, by city and state. He said there are additional sources of information here that can be brought to bear to answer Dr. Favata's issue, and questions about residential exposures.

Dr. Michalek then addressed Dr. Camp's issue about sigmoidoscopies. He said the study was going to consider that as a possibility for the next cycle. Dr. Camp said he didn't think about the Comparisons, of course. He said he was only concerned they were forcing the Ranch Hander to go out and get a sigmoidoscopy at his own expense when the physician at Scripps recommended it.

Dr. Harrison stated that he wasn't sure that many people do sigmoidoscopies anymore; they do flexible colonoscopes. After a discussion of occult blood screening and the magnitude of the job of doing

sigmoidoscopies on all subjects, Dr. Camp told the group that his remark had been misunderstood; that it related only to the veteran being told by a Scripps physician to get a sigmoidoscopy.

Dr. Michalek said Dr. Camp also brought up the idea of doing treadmill testing. COL Marden asked Dr. Camp if that also was in follow-up, and Dr. Camp said it was. The committee discussed the implications of what to do with a diagnosis resulting from a study physical requiring follow-up care.

Continuing with questions from Dr. Favata about the experience with the CAPI questionnaire, Dr. Michalek said it was an excellent tool for collecting data, and running it on a laptop proved convenient and time-saving. However, since the output format was not correctly specified, there were problems manipulating the data. He said that would be corrected for the next cycle.

Dr. Michalek stated that the baseline questionnaire remains unchanged. He discussed adding questions about drug use to future questionnaires. Another item brought up was the veteran's self-reported health status. He said they were going to try to find out what was driving these self-perceptions. Dr. Stoto suggested looking at use of the SF-36 form developed by a Boston group. Dr. Michalek said they would start to investigate the sed rate findings, at the suggestion of the committee. Dr. Michalek anticipated difficulties moving the sed rate from the general health chapter to the hematology chapter as suggested; Dr. Harrison said to leave it where it is in this report.

Chapter 16 - Endocrine. The reviewers of this chapter are Drs. Harrison and Stoto. Dr. Michalek made the presentation.

Dr. Michalek told the committee the Endocrine chapter reports a relation between diabetes, in all measures of dioxin; initial, categorical, and current. And that diabetic severity, fasting glucose, and A_{1c} hemoglobin was consistently related. He said he didn't know how to interpret the last finding.

Dr. Harrison started by saying he felt the introductory material regarding dioxin's effects in rats didn't matter much. Noting the passage describing several thyroid disorders found and that "the mix weighs against a relationship with dioxin," he felt dismissing this data was not a good idea. He said that the chapter has the problem of not having a more recent and timely literature review.

Dr. Harrison felt the way diabetes is classified in this study allows it to be compared to anything else, anyone else's studies. He said he doubted if any of the subjects were insulin-dependent, which is a specific technical term that's applied to diabetes; he said he felt very strongly that that needed to be changed to "insulin-requiring."

Dr. Harrison noted that the labeling of subjects as having Type II diabetes in the study is not supported well enough in the report, and Dr. Michalek said they will add additional data to the chapter. Dr. Harrison pointed to paragraph 3, page 163:

> ...consistent with dose response, a positive association between current body burden of dioxin and the development of diabetes, specifically in the later stages requiring oral hypoglycemic and insulin therapy.

He wondered, "if you take that a little further, does that mean that these people got fatter sooner? And hence became diabetic sooner, which means then that since they were diabetic longer, they're now requiring insulin" which he said would actually strengthen the relationship being developed.

The committee then discussed the study's analysis of A_{1c} hemoglobin. Dr. Michalek said the analysis of A_{1c} hemoglobin included everyone; namely, the non-diabetics and the diabetics.

Dr. Claxton asked if there were any sub-studies going on at all between Ranch Handers concerning these

results. Dr. Michalek said there were; one to determine a biological relationship between diabetes and dioxin.

In the second study, they are sending 30 non-diabetic Ranch Handers and matched controls to Little Rock, Arkansas to the VA Medical Center, to be tested for insulin sensitivity.

Dr. Delongchamp asked how you sort out the association between dioxin half-life in body fat from the association between diabetes and body fat. Dr. Michalek responded that in the current study they have matched individuals very tightly on body fat; they are identical in every way that appears to be relevant to the issue, and it's a matched pair analysis.

Dr. Stoto talked about how to take into account this three-way relationship between measured dioxin, body fat and diabetes. He said he thought that the models that are in this report are not as sophisticated as they can be.

Dr. Stoto had one technical comment on page 14, line 466, to clarify what it meant that they extrapolated the time in which diabetes would occur for non-diabetics. Dr. Michalek explained it was a censored survival analysis where if the event didn't occur, the time to onset was set to be the maximum, and censored at that point. Dr. Stoto said it needed fixing. Also, referring to the last two sentences, pages 175 and 176, Dr. Stoto felt a rewrite was in order.

Dr. Harrison said maybe people exposed to herbicides might tend to run a little higher blood sugar than the people that weren't exposed; but that both groups had the same amount of diabetes. Noting the report has the same number of people in each group, Dr. Harrison asked about the adjustments; were they using a fudge factor? Drs. Trewyn and Stoto said they were; a legitimate statistical practice.

Dr. Michalek said that, "based on those associations, we're motivated to ask Dr. Matsumura, is there a causal relation between diabetes and dioxin that motivated the adipose tissue study" which is being done right now. Dr. Harrison remarked that "In a sense, this is actually the observation that led to my being a part of this committee".

The committee then engaged in a discussion about the diabetes diagnosis used in the study. Dr. Harrison questioned the data showing out of the group of 200 Comparisons with diabetes, 75 of them have normal hemoglobin A_{1c}. Dr. Grubbs said the hemoglobin A_{1c} measurement is done on everybody, and the diabetes is based on two hour postprandial.

Dr. Check asked Dr. Harrison if he was questioning the validity of the diabetes diagnosis because he sees a surprisingly low number of elevated hemoglobin A_{1c}s; and he said yes, he was trying to figure out some other way of determining which of the group actually had diabetes.

Dr. Harrison said he would like to see the report saying that the diabetes diagnosis was based on World Health Organization, ADA, or other standard criteria. Dr. Check said that would remove that as a point of argument. Dr. Michalek said they would deal with it. Dr. Harrison said he wanted to think a little more about how the hemoglobin A_{1c} could be used.

Dr. Harrison stated he was very satisfied with the outcome in the endocrine assessment. He thought it could be made significantly better and very convincing.

The meeting adjourned at 4:40 p.m.

The Committee meeting continued in the same location on October 15, 1999, being called to order by Chairperson Harrison at 8:40 a.m.

OPEN COMMITTEE DISCUSSION

Dr. Harrison opened the second day of the meeting by reviewing the committee's discussion yesterday about the future of samples collected for the study, saying that "with some collaboration between the Air Force and the NIH or the Air Force and the scientific branch of the Army, to produce RFPs, Request for Proposals to cover the use of the unneeded samples that are presently simply being stored; and to also try and determine a mechanism to explain the association that we now feel exists between exposure to dioxin and diabetes mellitus type II."

Dr. Harrison read his proposed letter to Secretary Shalala. The committee discussed the wording of the letter. Dr. Stoto stated he would add a sentence in there saying that there may be other things in the data that are worth exploring as well. Dr. Michalek asked that the letter include the words, "Agent Orange related issues".

Dr. Stoto foresaw benefits of working with NIH researchers, who may see possibilities for these data. He felt the use of the phrase "unfortunate members of the Ranch Hands," was an unnecessary characterization. Dr. Harrison disagreed.

Presentation of Certificates of Appreciation
Retiring Committee Members Turner Camp, M.D., Irene Check, Ph.D., Delores C. Shockley, Ph.D., and Ronald W. Trewyn, Ph.D. were presented with certificates of appreciation by Rear Admiral Michael Blackwell, Chief of Staff, Office of the Surgeon General.

REVIEW OF THE AIR FORCE HEALTH STUDY CYCLE 5 CHAPTERS

Chapter 19 - Conclusions. Dr. Michalek presented a slide listing findings throughout the report: a significant number of Ranch Handers with increased dioxin; continued relation between body fat and dioxin and serum lipids and dioxin; and increased liver enzymes; platelets increased consistently across study cycles, including this one; consistent relations with diabetes, and a new finding in cardiovascular on the ECGs, evidence of prior heart attack, and a new finding in neurology of confirmed polyneuropathy.

Dr. Stoto wanted a change in the sentence: *In summary, the prevalence of endocrine disease remains similar in Ranch Hands and Comparisons.* Dr. Michalek said that while true, it was not a good summary.

Then 264; actually Section 19.5.8, which is the endocrine assessment, the last paragraph of that section. He said the one before that "basically says in summary there's nothing there." Dr. Stoto went on to say he was concerned about the sentence before that, which he felt should be struck. LTC Burnham and Dr. Harrison agreed.

Dr. Stoto went on to line 108 and 109, Section 19.5.1. He said he wasn't sure what that meant: *A finding of higher levels of dioxin in relatively obese participants on the basis of any health detriment is difficult to explain from* --. Dr. Michalek explained that doctor that wrote that is saying it's difficult for him to imagine a mechanism whereby dioxin would cause a disease that would also cause increased body fat, or which would be associated with increased body fat. Dr. Michalek said It contradicts the statements about diabetes, so maybe that sentence should be stricken, too.

Dr. Trewyn, remarking about Section 19.5.3, said the statement aligns 141 to 143, "inflammatory diseases as verified by medical record reviews were increased in Ranch Hands relative to Comparisons". Dr. Michalek stated that that means they have not studied that to their satisfaction, that what Dr. Trewyn is saying is true; that sed rate is correlated with inflammatory diseases in this group. If the statement is about us running

statistical analyses of inflammatory versus a sed rate he said has not been done.

Dr. Harrison asked Dr. Check, if she agreed we would expect that if inflammatory disease was present, that the sed rate should be elevated? She said yes. Dr. Michalek then said the word 'expected' should be in there.

Dr. Harrison noted that, "One of the problems with almost everything in here is that when you do find someone with something like an inflammation, you don't correlate whether that person's sed rate is increased." Dr. Michalek agreed, but said that "the ICD codes are given in the text; so what you're disagreeing with is the label we attached to that collection of codes." Dr. Stoto noted this comment was in the Neurologic section. Dr. Shockley pointed out that inflammatory conditions were based on the subject's report. Dr. Favata added, "and medical review."

Dr. Trewyn brought up the subject of elevated plasma liver enzyme levels, citing a paper he had been given about nonalcoholic steatohepatitis, which states that: it's an important differential diagnosis for asymptomatic patients with chronically elevated plasma liver enzyme levels, especially if obesity, diabetes, or hypolipidemia are present. And the people that are diagnosed with this apparently have a great chance to actually have then very significant liver problems subsequently. Colonel Marden stated that they go on to cirrhosis.

Dr. Harrison echoed the same point that Dr. Camp had made about some of the other findings, that this should be passed on to the subject's personal physician.

Dr. Harrison and Dr. Camp continued their debate over the idea that diabetes causes patients to gain weight. He stated that the tendency to be overweight is worsened by some of the changes that occur during diabetes, particularly treatment with antidiabetes medication, treatment with insulin. Dr. Camp said that some people who don't overeat get fat anyway. Dr. Harrison disagreed, saying: "If you gain weight, you have overeaten. Whether you have a low metabolism or whether you have a high metabolism is irrelevant to the fact that if you gain weight, you took in more calories than your metabolism required."

Future Directions. Dr. Michalek started the discussion by stating that in the next physical, they did not intend to continue half-life studies because the dwindling numbers of subjects means the statistical benefit is lessened considerably.

Dr. Favata inquired about continuing to get meaningful data, with the recognition that there's going to be increased mortality and morbidity among the study group.

Dr. Michalek pointed out, "We're going to try to address the number one issue on compliance that worries all of us; and that is the veterans that tell us they can't come because they're too sick." He worried about their staying home and expecting study personnel to come to them, not a desirable result. Also, we have to try to find some alternate measure of type A/B personality in order to do that covariate.

The other bias issue might be, Dr. Michalek pointed out, that a large part of the study's data collection is Ranch Handers bringing in photocopies of their personal physician medical records. So if you tell the doctor, "Gosh, diabetes is a major finding," that may focus his attention to diabetes and then downplay other things he might see in this person. The committee then got into a discussion of the relationship of the study to the primary care physician.

Dr. Delongchamp told the group that with the atomic bomb survivors have a card which says that they're a survivor, which then entitles them to medical benefits.

Dr. Harrison said he liked the idea of a card, encouraging the primary care physician to call and obtain past medical information. He said this would encourage the physician to call the study group when there's a

problem. Dr. Schwartz described a card that the VVA wants adopted for all veterans.

In response to Dr. Camp, Dr. Michalek explained that when a study subject stays home because he's too ill, it biases the study because getting the data from him at home is not the same as the workup.

Dr. Michalek brought up the problem with sending doctors to the veteran's homes; the men are spread all over the United States. He asked, isn't it infeasible from a licensing point of view? Colonel Marden: "It's a nightmare from a licensing standpoint." Several alternatives were discussed.

Dr. Delongchamp discussed the undesirability of data collected from a sick subject. He said what they we run into all the time is that once you've got this data, then you're always in this quandary about whether you want to use it or not.

Dr. Michalek said the study group wanted to do a complete review of all covariates and give a fresh look at how we adjust our analyses.

Dr. Miner informed the committee that the statement of work rewrite will start in the summer of the year 2000, and has to be completed probably by June of 2001, because that's the scheduled release of the RFP.

Dr. Schwartz described the air evac system available to veterans that could be used to get to the physicals; Dr. Camp mentioned the DAV transportation system available.

Dr. Harrison stated he felt a decision should be made whether or not all four models should be used in the upcoming year. He said he would like to see a spreadsheet on every Ranch Hander and Comparison ever in the study, which would allow one to see there were relationships between the findings, and further analysis. Dr. Stoto said that the fourth paragraph talks about doing that. He felt talking about disease outcomes across two or more clinical areas was difficult to do, but important. Dr. Harrison agreed.

Dr. Stoto felt it was important to recognize the importance of the statistical modeling about the dioxin elimination rate in relationship to body fat.

Dr. Stoto stated he wanted to consider dropping the dioxin measure on the people in the half life studies. Dr. Michalek said that on repeated measures, there is a lot of interest at CDC and elsewhere to get a second dioxin measurement on the control group, to see what happens to normal people over time.

Dr. Stoto observed that the study has multiple measures of diabetes and body fat for everybody, when we only had multiple measures of dioxin for some people. Dr. Michalek replied, that's a paper being working on right now. "We have multiple measurements, four measurements per subject for 500 Ranch Handers, and among those we have all the diabetic information, we have all their health information and the body fats."

He said if Dr. Stoto was recommending a second measurement, he would agree, too. But since the study is not budgeted to do that, support is needed.

Executive Summary.

Dr. Stoto said he thought it was nicely done, and he and Dr. Delongchamp had no complaints at all.

Dr. Trewyn wanted to make sure that on line 216 it will read "Incidence and prevalence of neoplastic disease" instead of "no significant difference in."

Dr. Harrison wanted the exact number of endpoints, referring to the wording "Statistical analysis of more than 225 health-related endpoints."

Dr. Harrison read the next sentence: "The finding of higher levels of dioxin in relatively obese participants on the basis of any health detriment is difficult to explain from a clinical standpoint and more likely related to the pharmacokinetics of dioxin." Dr. Michalek said it would be changed; the "clinical detriment" part will come out. Dr. Harrison said what it's supposed to be changed to is that the finding of higher levels of dioxin in relatively obese participants is not thought due to dioxin's effect on obesity.

Taking the phrase, "Ranch Hands had more inflammatory disease," a discussion ensued as to its meaning. Dr. Michalek said that included meningitis. Dr. Harrison said if it did, they should be two separate things.

Dr. Harrison read line 114: "Increases in tachycardia and other EKG diagnoses, such as preexcitation, were seen for Ranch Hands in the high dioxin category" and stated: Preexcitation syndrome, I think what you're referring to there is what's called Wolf Parkinson's White syndrome, which is a structural abnormality of the conduction apparatus of the heart, and it cannot conceivably be affected by dioxin.

Dr. Shockley read on line 128, "Do the future directions indicate that this" -- well, "it has potential association of dioxin that requires further observation." Dr. Michalek said that indeed the verbiage should be in the Future Directions section.

OPEN PUBLIC SESSION

Dr. Schwartz asked the committee when the report would be released; Dr. Michalek said sometime in January 2000. She tried to impress upon the committee the need for clarity in the wording of the report, and how important the words are to a diverse audience.

Dr. Camp and Dr. Schwartz discussed the decision of the NAS regarding diabetes. Dr. Michalek informed them of his recent presentation to the NAS on diabetes, and a few committee members expressed interest in getting a transcript of the talk. Dr. Michalek told he committee he could possibly email the transcript to them. Mr. Coene proposed to put in the record the names of individuals from whom we've received information and their statement, and put their names in the record and also attach their submissions as addenda to the Minutes of this meeting.

Colonel Marden pointed out that there were individual's medical records that needed to be safeguarded, and Mr. Coene said he would redact names.

OPEN COMMITTEE DISCUSSION (Continued)

Review of Air Force Press Release for 5th Cycle Final Report
The proposed press release was handed out to the committee. A discussion of the wording was held, and the draft was withdrawn to accomplish a rewrite.

ARMY CHEMICAL CORPS VIETNAM VETERANS HEALTH STUDY

Dr. Kang introduced this report to the committee as the first on the main study. He introduced the staff.

Dr. Harrison directed a question to either the Army Chemical Corps or the Air Force; he wanted to know the molarity of dioxin. He expressed some frustration at not knowing that; and Dr. Michalek promised to get him a response.

Dr. Rebecca Klemm had a packet of material passed out to the committee, and said she would give the committee an overview of the process, flow of information for the Chemical Corps project.

She told the committee that basically, it's a telephone interview with the people in which they answer things about their health conditions, their occupation, and their pregnancies from their female partners. Upon finding the subjects, there is an interview and medical record information is obtained. The study tracks down the medical records; people are selected for dioxin tests, blood is drawn and sent to CDC for analysis.

Dr. Klemm then gave a brief description of the populations. The first one is the entire population that the VA had consolidated to put together to create the study subjects. There are three: One, the total 5,285 Army Chemical Corps veterans in the study source population; Two, in the population that was provided to us to try and locate and interview; and the third is, where we were as of sometime at the end of August in terms of the interviews that had been completed.

Dr. Stoto asked a few questions about the populations; did they enter service at the same time, did they serve in the Chemical Corps at the same time. Dr. Kang explained the mechanism and said that the groupings were Chemical Corps Vietnam veterans and control Chemical Corps non-Vietnam veterans, and although all were Vietnam Era vets, they were purposely not matched year by year.

Dr. Stoto pointed out that the timing may be an important factor in the analysis, saying there were likely different exposures experienced by C.C. personnel in different years.

Dr. Kang responded that they were asking a detailed exposure history, including herbicides and other chemicals.

Dr. Harrison questioned the idea of taking the questionnaire of historical exposure and relating that to dioxin levels, to validate that the questionnaire really does give a good estimate of exposure, is a reasonable one. Dr. Kang said yes, referring to the pilot study in which a random sample of 50 Chemical Corps Vietnam vets and non-Vietnam vets' self-reported history associated with their body burden at the time we measure their dioxin level.

Mr. John Boyle spoke next about the location efforts made to find the study subjects. Beginning with an IRS records search, they did an initial phone (telephone) and address postal inquiry. Others were sought through Experian (credit reports). National change of address searches were done; direct directory assistance and use of data available on CD-ROMs. Telephone screening of all numbers to confirm correctness.

A short questionnaire was used to obtain phone numbers. Mr. Boyle went through the many types of efforts made to locate these individuals, then talked briefly about refusals and the reasons that were given.

Dr. Klemm described a blood draw from a sample of the located vets. She described their "wave" cycle.

Dr. Dalager told the committee about the analysis of the first 100 blood samples from the pilot study, and they had a consultant group from Johns Hopkins that took a look at those dioxin values and the measurements of exposure that were in the CATI questionnaire, and look at the possible correlations could be used as a surrogate for everybody in the study in terms of predicting their dioxin levels.

Ever-spray came up with a significant correlation with the dioxin levels. The strongest comparison is the ever-sprayed Vietnam to the never-sprayed non-Vietnam. In a response to LTC Burnham, Dr. Kang said the first report had been given to committee members at the initial meeting.

Dr. Stoto commented that these were amazing results. He felt there was an amazing consistency in odds ratios; that those suggested to him that there was some bias somewhere.

Dr. Dalager stated the study was particularly interested in liver conditions.

Dr. Harrison asked about the level of knowledge about the study, and Mr. Boyle said that the interviewers were blinded to the nature of the veteran's service and are not told the conditions the study is looking for.

Dr. Dalager told the group that another objective of the study was to look at reproductive outcomes.

Dr. Paxton then presented the committee with information about the progress of medical records retrievals, going through in detail the process of getting records. Dr. Klemm added a remark about the strong specificity required by the NPRC when requesting records, especially dates. It was discussed that the Ranch Hand Study uses NPRC also.

Dr. Magee went into the process of getting data from the records that had been obtained at that point. She discussed the results of investigating the newborn results.

Dr. Harrison discussed verification with Dr. Kang, suggesting that data developed in the Ranch Hand study may be of some use. Dr. Michalek suggested another source would be the Vietnam Experience Study. Dr. Harrison told Dr. Kang that the verification is a very important aspect that has to be solved.
The meeting adjourned at 2:12 p.m.

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Robert W. Harrison, M.D.   Date
Chair, Ranch Hand Advisory Committee

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Ronald F. Coene, P.E.   Date
Executive Secretary

Note: Copies of overhead transparencies, statements and other submitted materials are available from the Executive Secretariat..