hypothetical receptor site, an increase in body fat over time might either cause an increase in dioxin effect because of a greater volume of distribution or a decrease in dioxin effect because of a lesser concentration at the receptor site.

Statistical power is also an issue in a study of a population this size. A study with a population of 2,121 lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma) because such events are unlikely to occur in large numbers in a group this small. While certain occupational toxins have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually nonexistent in the absence of the toxin, other toxins merely increase the risk of nondiagnostic pathology. For example, this study would likely not discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology. By assessing the pathology observed in association with other known environmental risk factors (e.g., tobacco use, alcohol use) it is sometimes possible to provide a limit in the magnitude of effect missed; however, this study has inherent bounds in detecting modest increases in relative risk for infrequent pathology.

A final difficulty is the presence of a true association that is noncausal. An example might be a condition not caused by dioxin, but resulting in or from an altered dioxin half-life. In this case, a correlation might be high in the total absence of causality.

Clearly, there are many issues to be considered in interpreting these results. With these issues in mind, certain assessments were made by looking at a number of factors. Among these factors are longitudinal trends, biological plausibility, consistency with animal toxicology, the presence of a dose-response relation, and strength of association. But, meeting all of these criteria would not guarantee causality, nor would failing these criteria guarantee the lack of an effect. It can be argued, however, that the good faith application of these particular methods should be the starting point for generating hypotheses for experimental examination through in vitro and in vivo testing, as well as through further epidemiological analysis of these and other dioxin-exposed groups.

19.6 SUMMARY

Based on the findings of the 1997 examination, and subject to the qualifications considered above, the study investigators have drawn the following conclusions.

19.6.1 Diabetes

Consistent with previously reported results, current data indicate a significant and potentially meaningful adverse relation between serum dioxin levels and diabetes. A significant dose-response was found, with Ranch Hands in the high dioxin category exhibiting an increase in disease prevalence (relative risk=1.47, 95% confidence interval: [1.00,2.17]). The finding is supported by a dioxin-related increase in disease severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and α-1-C hemoglobin. Similar patterns were observed in 1987 and 1992.

19.6.2 Cardiovascular Abnormalities

Cardiovascular findings are mixed, but, in context with the increased cardiovascular mortality in nonflying enlisted Ranch Hands, are suggestive of an adverse effect of herbicide and dioxin exposure. As a group, Ranch Hands have experienced a statistically significant increase in the prevalence of heart disease (excluding essential hypertension) (relative risk=1.26, 95% confidence interval: [1.05,1.51]). The increase was more than doubled among enlisted flyers (relative risk=2.10, 95% confidence interval:

[1.27,3.28]) but not significantly increased among enlisted groundcrew (relative risk=1.10, 95% confidence interval: [0.84,1.42])—the military occupation with the highest dioxin levels. The prevalence of diagnosed essential hypertension and the percentage of Ranch Hands with ECG findings of prior myocardial infarction increased significantly with initial dioxin. Peripheral pulse abnormalities increased with dioxin levels in 1987 and 1992, but did not increase with dioxin levels in 1997. These findings, together with increased cardiovascular mortality in Ranch Hand nonflying enlisted personnel, suggest that herbicide or dioxin exposure may be related to cardiovascular abnormalities.

19.6.3 Peripheral Polyneuropathy

Although a common etiology is not apparent, a statistically significant increase in neurological disease appears in Ranch Hands historically, on physical examination, and as reflected in several of the composite polyneuropathy indices. Peripheral disorders, as verified by a medical records review, increased in Ranch Hands as levels of 1987 dioxin increased. Indices of bilateral peripheral polyneuropathy, confirmed by vibrotactile measurements in the feet, were significantly increased with initial dioxin level, significantly increased in the high dioxin category, and significantly increased with 1987 dioxin. These findings are new and appear consistent with polyneuropathies observed in studies of industrial exposure; however, the numbers of affected veterans are small and the clinical importance of the finding is uncertain.

19.6.4 Serum Lipid Abnormalities

There were consistent and significant increases in cholesterol, triglycerides, and the cholesterol-HDL ratio with initial and 1987 dioxin. HDL decreased significantly as dioxin increased. These findings also were observed in 1987 and 1992.

19.6.5 Liver Enzymes

Analysis of liver function reflected patterns that have been observed in prior examinations. Isolated group differences existed, but 1987 dioxin levels were strongly related to increases in hepatic enzymes, such as AST, ALT, and GGT and, as previously noted, cholesterol, triglycerides, and HDL. These results were consistent with an adverse dose-response and may be related to subclinical effects of unknown importance. Although hepatic enzymes increased with dioxin, there is no evidence of a corresponding increase in overt liver disease.

19.6.6 Malignant Neoplastic Disease

At the end of 15 years of surveillance, Ranch Hands as a group exhibited a nonsignificant increase in the risk of malignant neoplastic disease relative to Comparisons (relative risk=1.06, 95% confidence interval: [0.80,1.41]). Military occupation contrasts were inconsistent and, therefore, not supportive of an adverse effect of herbicide or dioxin exposure on the occurrence of malignancies. Ranch Hand enlisted groundcrew, the occupation with the highest dioxin levels and, presumably, the highest herbicide exposure, exhibited a decreased prevalence (relative risk=0.78, 95% confidence interval: [0.51,1.19]). Enlisted flyers (relative risk=1.63, 95% confidence interval: [0.91,2.92]) and officers (relative risk=1.14, 95% confidence interval: [0.79,1.65]), occupations with lower dioxin levels, exhibited nonsignificant increases in the prevalence of malignant disease. The risk of malignant disease was nonsignificantly increased among Ranch Hands having the highest dioxin levels (relative risk=1.01, 95% confidence interval: [0.66,1.57]). Longitudinal analyses found no significant group differences with regard to the

risk of malignancy and no pattern suggestive of an adverse relation between herbicide or dioxin exposure and the occurrence of malignant neoplastic disease.

19.7 CONCLUSION

In conclusion, diabetes and cardiovascular abnormalities represent the most important dioxin-related health problems seen in the AFHS. These two areas appear to have the greatest magnitude of effect in terms of quality of life and healthcare costs. Clearly, there are biological interrelations among both of these outcomes that make interpretations difficult. From a public health perspective, these two areas demand the greatest attention.

20 FUTURE DIRECTIONS

A careful review of the results of the last five physical examinations provides an opportunity to refine and focus the remaining examination of the Air Force Health Study. The current and prior examination outcomes have identified several medical tests requiring more intense evaluation and other analyses that can be reduced or eliminated in the 2002 study while still satisfying the study protocol.

The recently completed pharmacokinetic study of dioxin elimination in Ranch Hand veterans suggests that additional measurements per subject will not increase the precision of the estimated elimination rate. Thus, only those participants new to the study or those who have not already had a dioxin measurement will be invited to give blood for a dioxin assay in 2002.

In the final morbidity report, the Air Force intends to present a review of all herbicides sprayed by Operation Ranch Hand: 2,4-D, 2,4,5-T, picloram, and cacodylic acid, as well as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin).

The Jenkins Activity Survey, used to determine personality type (a covariate in the analysis of cardiovascular data), has become inappropriate to administer to elderly retired men because the survey questions refer to on-the-job situations. Alternative measures of personality type will be sought as a replacement for this instrument. In this regard, a thorough reassessment of covariate adjustments across all clinical areas will be made. New covariates may be added and out-of-date covariates may be dropped.

A new series of statistical analyses, accounting for disease outcomes that may cross two or more clinical areas, will be considered. The possibility of second-order effects will be studied for inclusion in the next report. A multifactor approach may be used to assess psychological outcomes, for example. Changes to or replacement of the current longitudinal analyses will be considered to explicitly account for loss-to-follow-up and time-dependent covariates.

Statistical modeling will be reviewed. In particular, Model 2 will be reassessed to address possible changes in the elimination rate with body fat. An analysis stratified by category of body fat measured in an earlier examination may be used. Interactions between extrapolated initial dose, disease outcome, and percent body fat will be considered as alternate approaches.

Special efforts will be made to address loss-to-follow-up and possible differential compliance due to ill health or other reasons that would bias the study. Expanded questionnaires may be administered to noncompliant veterans and consideration will be given to sending medical teams to the homes of veterans who report that they are too ill to attend the physical examination.

Analyses of disease prevalence among all study subjects, regardless of their compliance to the 2002 physical examination, will be accomplished and summarized in the final report.