Herbicide Exposure and Cancer

The case-control study in Kansas reported by Hoar et al[1] in this issue has importance beyond its population of agriculture workers to the highly controversial and adversarial issue of health effects associated with herbicide exposure in Vietnam. The well-designed and carefully executed Kansas study adds substantially to the cumulating body of evidence concerning the following question: Does human exposure to phenoxyacetic acid herbicides increase the risk of soft-tissue sarcomas (STS), Hodgkin's disease (HD), and non-Hodgkin's lymphoma (NHL)? The findings among Kansas farmers are in accord with "no" answers to the first two malignancies and a "yes" answer to the third.

See also p 1141.

Most relevant to the Kansas study are the series of case-control investigations undertaken by Hardell and colleagues[2-4] in rural Sweden in the mid- and late 1970s. Hardell's studies found highly significant relative risks, of magnitude fivefold and sixfold, for exposure to phenoxyacid herbicides in association with STS, HD, and NHL. Among the published epidemiologic studies, many regard the Hardell studies as the strangest in study design and certainly as providing the strongest available evidence of an association of herbicide exposure with the occurrence of cancer. However, selection bias, observation bias, and uncontrolled confounding loom as important points of vulnerability and, in fact, have emerged as the focus of sharp criticisms of the Hardell studies. In addition to critiques in the scientific literature, Hardell's studies have garnered considerable airing in the harsh give-and-take of the courtroom. Most recently, Hardell provided testimony in Australia to the Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam. The commission's Final Report[5] states:

> This absence of replication. [I discuss this below) the absence of specific outcome (ie, 12 types of soft tissue sarcoma, non-Hodgkin's malignant lymphoma and Hodgkin's Disease), admitted information bias, the presence of significant confounding factors, the unreliability of the exposure data and the other factors detailed above all indicate that the statistical associations asserted by Dr. Hardell are suspect. The Commission cannot, on the balance of probability, accept them as supporting an inference of causal connection between soft tissue sarcoma, malignant lymphoma and exposure to phenoxy herbicides.

With regard to STS, one other case-control study has appeared, namely, that of Smith et al[6] in New Zealand. Smith's findings conflict with those of Hardell and yield a negative result with an estimated relative risk of 13. Smith's study was designed to have adequate statistical power to detect a relative risk of roughly 3, if such a risk truly existed.

What now does the study by Hoar et al add to the evidence? Perhaps most noteworthy are the negative findings for STS and HD. As a crude tally, this makes a score of two negative (Smith and Hoar) vs one positive (Hardell) study for STS and a tie of one each negative (Hoar) and positive (Hardell) study for HD. With regard to NHL, the score stands at two positive studies (Hoar and Hardell).

More important and relevant, however, are how the Hoar and Hardell studies compare methodologically. Does the Hoar study better withstand the critical onslaught that has besieged Hardell's studies? Of course, the Hoar study has undergone only the intensity of *JAMA*'s peer review process and has not (at least to my knowledge) been subject to the rigors and scrutiny of courtroom debate. Let me attempt to probe some methodological contrasts of the two studies.

The Hoar study, like Hardell's, has the strength of case ascertainment with a population-based tumor registry along with independent pathological review and confirmation of disease. The Hoar study is considerably larger than Hardell's, with nearly twice the number of cases of malignant lymphoma and three times the number of controls. Thus, Hoar's study has considerably greater statistical precision and statistical power to detect differences. Both studies employed population-based controls, using living controls for living cases and deceased controls for deceased cases. As such, both studies had to rely in part on next of kin's reporting of exposure status.

In contrast to what has surfaced regarding the procedure

for conducting the interviews in the Hardell studies, the Hoar study involved experienced and trained interviewers who followed a detailed, predetermined interview protocol (Dr Hoar, oral communication. April 1986). The interviewers knew that the study concerned chemical exposure, but were unaware that the study's major hypothesis dealt with exposure to phenoxyacetic acid herbicides. Although the Hoar study intended blind interviews in regard to the subject's status as a case or control, information provided during the conversation often indicated clearly to the interviewer the subject's disease classification. Another advantage of the Hoar study is that the interviewing, conducted mainly in 1983, occurred at a time when there was no particular local media attention to herbicide exposure and cancer risk. Although there was considerable national concern at that time with Agent Orange exposure in Vietnam, the media in Kansas in 1983 did not shine the public spotlight on farmers' herbicide exposure and their risks of these three malignancies. Thio is very much in contrast to the timing of the Hardell studies during a period of intense media attention in Sweden and Dr Hardell's prominent role in the media with his taking of an advocacy position. Clearly, the interview methodology and the climate of the Hoar study make information bias a much more unlikely explanation for their findings compared with the Hardell studies.

Another strength of the Hoar study is the validation of a sample of self-reported exposure by a survey of suppliers. No differences were found in the corroboration among controls and each of the STS, HD. and NHL cases. Of course, not all subjects had such validation of their exposure status. But, what was done *suggests* the unlikely event of large differences between cases and controls in their accuracy of reporting exposure.

The Hoar study considered and reasonably ruled out confounding effects of exposure to other herbicides, insecticider, fungicides, nonfarming exposures, and both the known and alleged risk factors for each of these *three* malignancies. Another strength of the Hoar study is the consistent dose-response relationship for NHL according to the nature, intensity, and duration of exposure. The specificity of the findings of an association with one *cancer* and no association with the other two is another relative strength of the Hoar study compared with the Hardell studies. in which the results were an across-the-boards elevated relative risk for each of the three cancers.

Limitations of the Hoar study include those inherent with case-control studies that rely on subjects' and next of kin's recall of exposure status. Faulty recall leads to misclassification. If this occurred equally among cases and controls, the study would underestimate and thus possibly miss a true increase in risk If it occurred differentially, this could lead to bias. As indicated above, however, bias due to differential recall of cases and controls seems unlikely in the Hoar study.

Another limitation characteristic of observational epidemiologic studies is the possibility of uncontrolled confounding, particularly with diseases whose epidemiology is unclear. This, of course, remains a possibility and to some extent constitutes the frontiers of our knowledge of the etiology of these three malignancies.

Also, one cannot rule out entirely the possibility of chance as an explanation for the findings.

All in all, however, the Hoar study does indeed provide a much firmer and tighter body of scientific evidence than do the Hardell studies.

What supporting or contradictory evidence exists from other epidemiologic studies? None of the several industrial cohort mortality studies of dioxin exposure has resulted in a noted perturbation in the frequency of deaths from these cancers. The one published cohort study of Agent Orange exposure in Vietnam, namely, the US Air Force Ranch Hand Study,' has to date not detected any increase in incidence or mortality from these cancers. But, the industrial studies generally entail extremely small sample sizes that almost totally lack adequate statistid power to detect meaningful increases in risk. Even the Ranch Hand Study with its defined cohort of roughly 1200 exposed individuals lacks statistical power to detect an increased risk of these malignancies. whose incidence rates in the general population are low. Thus, the negative findings of the published cohort studies, though at first blush are corroborative of the negative case-control studies, provide little substantiation because of their inherent small sample size and limited statistical power.

Several proportional mortality studies have appeared in "bonus" states (ie, those states that offered a bonus in terms of a financial incentive to men who enlisted for Vietnam service). Most notable is the Massachusetts study' that found nine deaths from STS among Vietnam veterans compared with only one expected. Interestingly, the Massachusetts *study* lacked sufficient numbers to investigate proportional mortality for NHL (Richard Clapp, MPH, oral communication. March 1986). In contrast to case-control studies. proportional mortality studies have even greater vulnerability to forces of selection, observation, and confounding biases. Furthermore. these state studies have three additional serious limitations: (1) the quality and accuracy of the dath certificate diagnosis of these malignancies (2) the effects of migration resulting from the sizable numbers Of veterans who, subsequent to their military service, emigrated from the state and thus do not appear on the state's death tapes, and (3) the fact that none of these studies determined decendents' herbicide exposure but dealt only with their service in Vietnam. Thus, whatever the findings of the proportional mortality investigations, they add Little if any substantive analytic evidence to the fundamental question of cancer risk as a result of herbicide exposure.

Is more pertinent evidence *on* these cancer risks in the *offing?* Ye! To my knowledge two additional case-control studies of these cancers are under way, each involving a considerably larger number of cases than any of the studies presently at hand, including the study by Hoar. Both studies in progress involve herbicide exposure in Vietnam as assessed by the Environmental Support Group of the Armed Forces with tlk use of available military records on troop locations in conjunction with records of berbicide sprayings. The first of these studies, tentatively scheduled for completion in the summer of 1986, is a joint effort of the Veterans Administration and the Armed Forces Institute of Pathology (Han Kang, PhD, oral communication, March 1986). It involves STS only and entails nearly 300 confirmed cases ascertained through the Armed Forces Institute of Pathology and approximately 600 controls. The study *was* designed to have good statistical power to detect a twofold increase in

relative risk. The second study is the Selected Cancers component of the massive Centers for Disease Control's Epidemiologic Studies of the Health of Vietnam Veterans. The Centers for Disease Control's selected cancers study, scheduled for completion in the fall of 1989, entails enrollment of approximately 400 incident cases of STS and 1400 malignant lymphomas (HD and NHL) during the period Dec 1, 1984, through Nov 30, 1988 (Edward Brann, MD, oral communication, March 1986). Case ascertainment is through six population-based cancer registries in the United States that, interestingly, includes the registry in Kansas. The studies by the Centers for Disease Control have been designed to have good statistical power (namely, 80% or higher) to detect a true twofold increase in relative risk for each of these three cancers, as well as for other "selected" cancers (ie, primary liver, nasal and nasopharyngeal).

Where does this leave us now in regard to herbicide exposure and cancer risk? The Hoar study in Kansas, in conjunction with the Smith study is New Zealand, tends to shift our concern toward a somewhat lesser interest in STS and a greater interest in NHL. I note that in Hardell's study of malignant lymphoma,' only one short paragraph at the end of the "Results" section indicated that the elevated risk was the same for HD and NHL; otherwise, Hardell's analysis considered the two malignancies together as "malignant lymphoma." Hoar rt al have now focused attention specifically on NHL risk.

Perhaps the question will never be answered entirely satisfactorily. Whatever direction future results take, it is clear that the report by Hoar et al will have considerable use—and the attendant and inevitable abuse—in the continuing scientific controversy, public debate, and legal battles regarding herbicide exposure and cancer risk.

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