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REVIEW OF THE AUSTRALIAN VIETNAM VETERANS BIRTH DEFECTS STUDY

by the Science Panel of the Agent Orange Working Group (Cabinet Council)

Introduction: The purpose of this paper is to review the methodology, statistics and conclusions of the Australian Study of Congenital Anomalies. The significance of the Australian study and its relevance to the U.S. veteran will also be discussed.

The Australian Study

Purpose: The purpose of the Australian Study of Congenital Anomalies and Vietnam Service was to determine whether the risk of major congenital anomalies is greater among children of Vietnam veterans than among other children born in Australia or among children of Australian veterans who did not serve in Vietnam. The study is limited to evaluation of major birth defects and does not include information about fertility or other adverse reproductive outcomes. It does not, nor was it intended to address the potential effects of exposure to specific chemicals, such as Agent Orange, while in Vietnam.

Study Methods: The study was carried out by investigators of the Australian Commonwealth Institute of Health during 1981-1983. Cases were obtained from 34 hospitals and 4 cytogenetic laboratories which cover approximately one-half of the Australian population. The study population consisted of 8517 infants with

birth defects and 8517 infants without birth defects who were matched individually for date of birth, hospital of birth, mother's age, and hospital payment status. The reason for matching was to make the members of each pair as similar as possible with regard to other factors which may influence the risk of birth defects.

For each pair, the researchers determined whether the infants' fathers served in Vietnam. They then compared the number of pairs in which the father of the infant with a birth defect served in Vietnam, but the father of the 'normal' infant did not, with the number of pairs where the father of the infant with a birth defect did not serve in Vietnam, but the father of the 'normal' infant did. If service in Vietnam was a risk factor for birth defects one would expect to find many more pairs where the father of the infant with a birth defect served in Vietnam than pairs where the father of the 'normal' infant served in Vietnam.* The investigators state that the overall finding for the study provides, "...no evidence that army service in Vietnam has increased the risk of the birth of a child with an anomaly" and additional analyses of different parts of the data, including adjustments for other risk factors, do not alter this finding.

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*This is a standard technique used in matched-pair analysis. Those pairs which both the malformed and the healthy child had fathers who did or did not serve in Vietnam provide no information either for or against an association between service in Vietnam and fathering a malformed infant.

Science Panel Evaluation

In order to evaluate the Australian Study, we examined potential problems with the selection of study infants, determination of fathers' military experience, and/or inadequate adjustments for other risk factors for birth defects. Recognition of potential problems helps the reviewer to assess the strength of the findings and to determine the likelihood that similar findings would be observed in comparable studies.

The selection of study infants: The degree of ascertainment of all children with congenital anomalies in the selected hospitals was not established. Although direct comparison of the prevalence of congenital malformations by hospitals would be most useful, the seemingly low number of confirmed cases of birth defects from some hospitals suggests that ascertainment varied considerably. It was noted that several hospitals had incomplete record keeping, some cases were picked up through the cytogenetic labs but not by the hospital records, a variety of record sources were utilized, and some hospitals lacked disease indexes for all years. Even under the best of circumstances all of congenital anomalies will not be identified before leaving the hospital.

Under-ascertainment of births to veterans is suggested by the lower-than-expected proportion of servicemen included in the study (although this could also be the result of decreased fecundity). If there was a tendency for hospitals serving large numbers of servicemen (and veterans) to have poor ascertainment of birth defects, with correspondingly fewer controls,

this could lead to an underestimate of the proportion of veterans among fathers of healthy controls as well as affected children. Matching controls to cases by hospital of birth should have eliminated bias due to differential ascertainment among hospitals.

However, if a father's veteran status directly or indirectly affected the chance of his child with a birth defect being included in the study, the proportion of veterans among case fathers would be affected, and the relative risk might be inappropriately estimated. As this may be more or less evident among cases ascertained under different conditions, separate analyses of the data for cases diagnosed before and after leaving hospital, among stillbirths, among cytogenetic laboratory submissions, etc., would be useful to assess possible bias from this source.

Information was not obtained equally for cases and controls. For example, father's age and/or birthplace was missing for approximately 5% of cases but only 0.3% of controls. While small numbers of missing data for these items probably have little effect, it does suggest differences in the quality of data for cases and controls. In particular, 10% of case fathers were apparently identified from records other than a birth certificate and an unknown number were unidentifiable, while virtually all healthy babies' fathers were identified from birth certificates. Thus, if his veteran status affected a case baby's father's chance of being identified, a bias similar to that for ascertainment of cases could be introduced. Although the relatively small number of cases involved indicates that this is not a major source of error, a separate

analysis of those case-control pairs for which fathers were identified from birth certificates in both the case and first-choice control would be more convincing.

Determination of fathers' military status: Determination of veteran status was made by taking the father's name from the child's birth certificate or other records, determining his birthdate from various records, matching names and birth dates to lists of servicemen and veterans for military status, and determining Vietnam status from Army service records. Pilot studies demonstrated problems with such record linkage but the investigators were nonetheless able to designate virtually all study subjects as Vietnam veterans, non-Vietnam veterans or non-Army persons. Misclassification of the veteran's status in a nonrandom manner among cases and/or controls could severely bias the data, and precautions to avoid this consisted of determining the military service status of each study subject's father without knowledge of the case/control status of the subject. The 11 case and 4 control fathers who could not be unambiguously classified as veterans or not were included in a "worst case" analysis which did not change the conclusions of the study. While there is no reason to believe that the study was biased by misclassification of veteran status of subjects' fathers, the power of the study to differentiate between alternative hypotheses would be lessened if much misclassification had occurred. In particular, the fathers of 15 malformed and 13 healthy children first served in Vietnam after conception of the child. The results of separate analyses which logically excluded them as Vietnam veterans (for the purposes of this study) do not alter conclusions. However, this does reduce the proportion of Vietnam veterans among healthy

controls and thus the attained power of the study to detect a relative risk of at least 1.5 is less than the 90.5% stated in the report.

Adjustment for other risk factors: The investigators matched infants with and without birth defects on the four variables listed above and adjusted for other risk factors in the analysis. Initial steps of the statistical analysis examined the association of each of several potential risk factors separately with the disease status (case or control). Sex of child, mother's age, birth place of father, plurality of birth and some interactions were found to be significantly associated with birth defects. Logistic regression was then used to manipulate combinations of these variables and estimate the association between veteran status and birth defects with adjustment for effect modifiers. Results were similar to those for the unadjusted analysis.

This method, while commonly used, has been criticized because it does not test the relationship of potentially confounding factors to both exposure and disease. Current methodology suggest that strict adherence to significance tests for the identification of potentially confounding variables may not be advisable. Decisions for adjustment might better be cased on biological considerations.

Clearly, unmeasured potential confounders cannot be used for adjustment. For example, in the present study, Vietnam service is confounded by having served in the Army per se and no analytical technique could have been used to determine if service in Vietnam were a risk factor for fathering a child with a birth defect unless veterans who had not served in Vietnam were included in the

study. Some potential confounders such as alcohol consumption and occupation were not measured due to the nature of the data sources and it cannot be determined whether the findings would be the same if such additional potential confounders had been examined.

Science Panel Conclusion

This study has demonstrated with a good deal of sensitivity that there does not appear to be an overall increase in major congenital anomalies among offspring of Australian men who served in Vietnam. It does not address individual exposure to chemical agents such as Agent Orange, nor specific defects. The power to detect a relative risk greater than 1.5 is based upon all congenital defects and appears sufficiently sensitive. However, the more plausible biologic hypothesis implicating a particular exposure to a particular defect cannot be tested in this study because the numbers of infants with specific birth defects are too few. While it is important to be aware of the potential problems affecting the outcome of this study, it is unlikely that these problems dramatically affected the investigators' final conclusions. We find that the conclusion of this study is consistent with the data presented and the investigator's objectives.

Relevance to U.S. Veterans

Congenital malformations are a major concern of all servicemen who served in Vietnam. The relevance of this study to the U.S. veteran depends upon the similarity between American and Australian servicemen and their experience while

in Vietnam. Among the many variables to be considered are the location in which he served, dates in that location, and exposures within the environment at those specific times and locations. Many veterans are concerned about exposures to Agent Orange and other herbicides, antimalarials, and other medicines, alcohol and other drugs, and stress. The Australian study did not examine individual risk factors incurred while in service and no data were available to establish an exposure classification for chemicals such as Agent Orange. Therefore one can only say that the Vietnam "experience" of Australian troops does not appear to have increased the overall risk of birth defects for them.

Presently, the CDC Birth Defect Study is nearing completion of its data collection phase. Analyses similar to those performed in the Australian Study will be conducted. In addition, it is planned for the analysis of these data to include more information regarding potential exposures servicemen may have had, since information will be obtained in a telephone interview as well as from service records.