Counterpoint: Responding to Inadequate Critique of Birth Defects Paper

David N. Cowan,1 Gregory C. Gray,2 and Robert F. DeFraites3

Before responding to Haley's critique (1) of the three papers recently published in the New England Journal of Medicine (2–4), we would like to place our research in perspective. We conducted an exploratory comparison of the available medical data for two large cohorts to see if there was an association between Gulf War service and the risk of birth defects. As pointed out by Wegman et al., there is a "serious lack of information about risk factors" (5, p. 704), and so our study was conducted without specific environmental exposure hypotheses. It was an initial, rather than a final, evaluation of reproductive outcomes among Gulf War veterans.

Haley goes into great detail about why he believes the findings of our report are not valid, including developing and arguing a complex scenario of "given," "if," and "then" statements. A review of Haley's argument regarding the birth defects study is in order.

The first "if" statement ("The wartime exposures (e.g., chemical or biologic toxins) in deployed veterans caused both the symptoms of the Gulf War syndrome and birth defects" (1, p. 320)) is offered with no consideration for biologic plausibility or even speculation regarding which exposures might possibly cause both a "Gulf War syndrome" and birth defects. Future research efforts would benefit if Haley could offer a hypothesis regarding a Gulf War exposure that might cause both a newly described chronic condition and paternally mediated teratogenesis. We hope he will be forthcoming, particularly since the role of and mechanism for male-mediated teratogenesis remain unclear. Haley's argument also has errors in logic. In this "if" statement, he lists the "Gulf War syndrome" separately from birth defects, while in the following paragraph he redefines them as one and the same ("... birth defects are part of the Gulf War syndrome ..." (1, p. 320)), which forces the "if" statement to be true. This has implications for his next "if" statement as well, in that it implies, with no supporting data, that persons with an increased risk of birth defects left the military at a higher rate than did persons without increased risk.

The second "if" statement ("The symptoms of the Gulf War syndrome caused many affected veterans in the deployed group to be separated from active duty prematurely during the postwar period of follow-up" (1, p. 320)) deserves further examination. Haley uses separation data from the hospitalization study (2) to criticize our birth defects study (4). This is inappropriate because the two studies' cohorts differed in composition and had different start and stop dates for subject follow-up. Haley apparently failed to note that the birth defects paper (4) reported loss from active duty at two dates (September 1992 and September 1993) and not the date reported in the hospitalization paper (December 1993) (2). Haley (1) attempts to validate the second "if" statement utilizing the December 1993 data. At the two September dates we reported, there was little difference in attrition; that is, the relative risks for male Gulf War veterans were 1.01 and 1.04, respectively, and among women the relative risks were 0.93 and 0.99. Our study evaluated births only until the end of September 1993; attrition after that date is irrelevant. Finally, in spite of Haley's convoluted logic regarding the reasons for leaving military service, Gray et al. (6) provide detailed information indicating that undiagnosed Gulf War-related illnesses are not likely to be causing substantial attrition among deployed veterans.

Because the first "if" statement is purely speculative and the second "if" statement is false, Haley's two "then" statements ("Failure to include records of births and birth defects from nonmilitary hospitals in the study preferentially excluded the birth defects caused by the war" (1, p. 320) and "Finding no difference in the rates of postwar birth defects in the deployed and nondeployed groups would not rule out an excess of birth defects caused by exposures in the war" (1, p. 320)) are not true.

Haley apparently also misunderstands our comments regarding births identified but not taking place
in military hospitals. There was concern that births occurring during the follow-up period but occurring in civilian hospitals may have been at high risk for defects and that, if these births were differentially associated with deployment, then they could have been a source of bias. However, we found that births to male Gulf War veterans were slightly less likely to have occurred in civilian facilities, and essentially all births to female veterans, both deployed and not, occurred in military facilities (4).

Furthermore, Haley appears to have ignored our dose-response (risk by time-in-theater) analyses (4, table 3 and text). If there were some teratogen present in the Gulf War environment, regardless of whether it also caused symptoms of the “Gulf War syndrome,” there would likely be some dose-response association; for example, longer or higher cumulative levels of exposure, or greater opportunity to experience some threshold level of exposure, might result in more birth defects. We found no association with time-in-theater among deployed service members, no matter how we evaluated the data for two definitions of birth defect. These analyses, which include an internal control of exposure, should relieve any concerns regarding comparisons between deployed and nondeployed service members.

Haley calls for future studies to include all birth defects. All recorded birth defects were captured and included in our report. Furthermore, although we included tables (4, tables 5 and 6) with birth defects comprising 5 percent or more of all serious defects (and found no significant increases among Gulf War veterans), we also evaluated but did not publish all specific groups of defects occurring among our population. Even among the rare events, there were no significant or substantial associations with Gulf War service.

Finally, Haley calls for additional studies that capture all births occurring among deployed and nondeployed members, including those among persons leaving active duty. Logistically, it would be very difficult to conduct such a historical longitudinal study, particularly in the absence of a specific, testable exposure or biologically plausible defect hypothesis. Anticipated difficulties in subject tracing, locating, and contacting, identifying births, obtaining informed consent to contact hospitals and physicians, and ascertaining defects from data recorded in a myriad of different fashions may well introduce serious biases. However, other studies utilizing other methodologies have been completed or are underway. These include the recently published paper evaluating Goldenhar’s syndrome (7); an examination of births among both separated and active duty personnel in both military and civilian facilities occurring in seven states that maintain active case ascertainment programs for birth defects (8); a health study underway by the Department of Veterans Affairs that will capture reproductive outcomes in a nationwide sample of veterans (Han Kang, Environmental Epidemiology Service, Department of Veterans Affairs, personal communication, 1997); a study of the health of female veterans (9); and a study underway in London evaluating birth defects among children of British Gulf War veterans (10).

We acknowledge that it has not been “proven” that children of Gulf War veterans are not at higher risk of birth defects, even though none of the peer-reviewed studies completed to date has identified a significant association (4, 6, 11). Furthermore, it is possible that there are some rare defects that may be associated with some specific exposures occurring in the war. However, if the ongoing studies fail to detect such an association, one must question whether it is the most appropriate or best use of limited resources to continue to pursue this area of research, particularly in the absence of a clearly defined hypothesis regarding measurable exposures and specific birth defects.

REFERENCES