Table 34. Number of Reported *Infant Deaths*, Crude Rates Per 1000 Live Births Among Vietnam and Non-Vietnam Veterans, and Crude and Adjusted Odds Ratios for Children of Vietnam Veterans, by Component of Vietnam Experience

| | | | | | Multivariate Results | | | |
| | | | Crude Results | | Model 1[a] | | Model 2[b] | |
Experience	Rate	No.[c]	OR	95% CI	OR	95% CI	OR	95% CI
				Non-Vietnam				
	11.8	139	—	—	—	—	—	—
				Vietnam				
Reported Combat Exposure[d]								
Low	11.0	34	1.0	—	1.0	—	1.0	—
Mid	13.8	42	1.3	0.8-2.0	1.0	0.6-1.6	1.0	0.6-1.6
High	11.4	33	1.0	0.6-1.7	0.7	0.4-1.2	0.7	0.4-1.2
Very high	11.8	39	1.1	0.7-1.7	0.6	0.4-1.1	0.7	0.4-1.2
Reported Drug Use in Army								
None	12.1	113	1.0	—	1.0	—	1.0	—
Marijuana only	12.8	29	1.1	0.7-1.6	1.0	0.6-1.5	1.0	0.6-1.5
Hard drugs	9.0	9	0.7	0.4-1.5	0.7	0.3-1.4	0.7	0.3-1.4
Reported Herbicide Exposure[d]								
None	8.2	45	1.0	—	1.0	—	1.0	—
Low	15.1	58	1.9	1.3-2.7	1.9	1.2-2.9	1.9	1.2-2.9
Mid	14.1	38	1.7	1.1-2.7	2.0	1.2-3.1	2.0	1.3-3.3
High	18.1	11	2.2	1.1-4.3	2.7	1.4-5.4	2.8	1.4-5.5
Year of Entry into Army								
1965-66	11.6	52	1.0	—	1.0	—	1.0	—
1967-69	12.7	90	1.1	0.8-1.5	1.1	0.8-1.6	1.1	0.7-1.5
1970-71	9.3	10	0.8	0.4-1.6	0.8	0.4-1.6	0.8	0.4-1.7
Primary Military Occupational Specialty								
Nontactical	11.1	91	1.0	—	1.0	—	1.0	—
Tactical	13.6	61	1.2	0.9-1.7	1.3	0.9-1.9	1.2	0.8-1.8

[a] Model 1 contains the primary covariates. Each multivariate result is also adjusted for the other components of the Vietnam experience. No interactions were assessed.
[b] Model 2 contains the primary and secondary covariates.
[c] Sum of cases over strata may be less than total numbers presented in previous analyses because of missing values for covariates.
[d] See Volume II, Appendix E, for methods used to create combat and herbicide exposure indices.

4.3 ANALYTIC METHODS

4.3.1 Multiple Comparisons

The association between the Vietnam experience and reproductive and child health was evaluated for many different outcomes. As suggested by Rothman (1986), we did not adjust for "multiple comparisons." Instead, we emphasized confidence intervals rather than tests of statistical significance and reported positive as well as negative results. Moreover, we observed a pattern in which a disproportionate number of odds ratios were greater than 1.0. This pattern is not likely to be due to chance or to the large number of comparisons made.

4.3.2 Multivariate Modeling Strategy

We did not attempt to identify a "best" model for each outcome. Thus, a priori confounders remained in the models regardless of their statistical significance; statistical interaction or product terms were removed unless they were statistically significant at the 0.01 level; and tests for interaction were performed only when the number of cases was sufficient to allow a modestly stable estimate of the interaction term. The potential gain in

Table 35. Number of Reported *Miscarriages*, Crude Rates Per 100 Total Pregnancies Among Vietnam Veterans, Veterans With Other Foreign Service (Germany or Korea), and Veterans With No Foreign Service, and Crude and Adjusted Odds Ratios

| | Vietnam | | Non-Vietnam | | Crude Results | | Multivariate Results | | | |
| | | | | | | | Model 1[a] | | Model 2[b] | |
Comparison	Rate	No.	Rate	No.	OR	95% CI	OR	95% CI	OR	95% CI
Vietnam versus Germany/Korea	10.4	1566	8.8	695	1.2	1.1-1.3	1.2	1.1-1.4	1.2	1.1-1.3
Vietnam versus United States service only	10.4	1566	8.5	495	1.3	1.1-1.4	1.3	1.2-1.5	1.3	1.1-1.4

[a] Model 1 contains the primary covariates. No interactions were assessed.
[b] Model 2 contains the primary and secondary covariates. No interactions were assessed.

precision and parsimony associated with a "best" model could have required preservation of a different "final" model for nearly every outcome. The greatly increased complexity would have overshadowed the gain in parsimony, given the large number of health outcomes evaluated. Furthermore, precision of point estimates were generally not affected appreciably by inclusion of all covariates in the models because of the large study size and the balanced distribution of the covariates.

4.4 INTERPRETATION OF RESULTS

The overall increased reporting by Vietnam veterans of a wide range of health outcomes in their children is difficult to interpret. It is, however, consistent with their reporting more adverse events with regard to their own health (Volume II). These findings suggest a real difference in the way Vietnam veterans perceive and report their own health and the health of their children.

The most serious concern in interpreting the results from the VES interview is the quality of the reported information on reproductive and child health. The observed excess in reported events could be due to differences between Vietnam and non-Vietnam veterans in the manner, extent, and accuracy of reporting. There is some evidence to support a hypothesis of differential reporting (*i.e.* information bias) in the two veteran cohorts.

First, the increased reporting by Vietnam veterans is nonspecific—that is, it pertains to most of the child health outcomes studied. This nonspecific increased reporting is also seen for a wide variety of outcomes pertaining to the veterans' own health (Volume II). Given that

Table 36. Number of Reported *Stillbirths*, Crude Rates Per 1000 Total Births Among Vietnam Veterans, Veterans With Other Foreign Service (Germany or Korea), and Veterans With No Foreign Service, and Crude and Adjusted Odds Ratios

| | Vietnam | | Non-Vietnam | | Crude Results | | Multivariate Results | | | |
| | | | | | | | Model 1[a] | | Model 2[b] | |
Comparison	Rate	No.	Rate	No.	OR	95% CI	OR	95% CI	OR	95% CI
Vietnam versus Germany/Korea	9.9	126	11.2	77	0.9	0.7-1.2	0.8	0.6-1.1	0.8	0.6-1.1
Vietnam versus United States service only	9.9	126	10.7	54	0.9	0.7-1.3	0.9	0.6-1.2	0.9	0.6-1.3

[a] Model 1 contains the primary covariates. No interactions were assessed.
[b] Model 2 contains the primary and secondary covariates. No interactions were assessed.

Table 37. Number of Children With Reported *Birth Defects*, Crude Rates Per 1000 To al Births Among Vietnam Veterans, Veterans With Other Foreign Service (Germany or Korea), and Veterans With No Foreign Service, and Crude and Adjusted Odds Ratios

| | Vietnam | | Non-Vietnam | | Crude Results | | Multivariate Resu ts | | | |
| | | | | | | | Model 1[a] | | Mo Jel 2[b] | |
Comparison	Rate	No.	Rate	No.	OR	95% CI	OR	95% CI	OR	95% CI
Vietnam versus Germany/Korea	64.6	826	49.7	341	1.3	1.2-1.5	1.3	1.1-1.5	1.3	1.1-1.4
Vietnam versus United States service only	64.6	826	49.3	249	1.3	1.2-1.5	1.3	1.1-1.5	1.3	1.1-1.5

[a] Model 1 contains the primary covariates. No interactions were assessed.
[b] Model 2 contains the primary and secondary covariates. No interactions were assessed.

Vietnam veterans reported an excess of most personal and child health conditior s about which they were asked, it is difficult to attribute this degree of nonspecific excess reporting to an actual exposure or set of exposures.

Second, in the case of birth defects, the rate is significantly elevated among c ildren of Vietnam veterans who were conceived before their father's assignment to Vietr am. This suggests that if the excess is real, it is not related to service in Vietnam, and if the excess is due to differential reporting, the bias is not restricted to children born after servic .

Finally, on the one hand, there is a strong association between most of the reported outcomes (miscarriages, birth defects, serious health problems, and infant mor ality) and self-reported exposure to herbicides in Vietnam. Vietnam veterans who believe hey were exposed to herbicides report more child health problems than men who were uncertain about exposure or did not think they were exposed. Furthermore, within the "exposed" group, there is a gradient with the veteran's assessment of *degree* of exposure. Or the other hand, within the subgroup of men who did not admit to any herbicide exposure, the reporting of outcomes resembled that of non-Vietnam veterans. The association betweeri reported outcomes and reported exposure to herbicides in Vietnam is also seen for veterans' health outcomes (Volume II).

The findings from a recent study in which current dioxin (2,3,7,8-tetrachlorodibenzo-para-dioxin) body burdens in Vietnam and non-Vietnam veterans were assessed (Centers for Disease Control, in press) suggest that self-reported herbicide exposure may not be a valid estimate of actual herbicide exposure. Among Vietnam veterans, there was no evidence of

Table 38. Number of Children With Reported *Serious Health Problems*, Crude Rates Per 1000 Live Births Among Vietnam Veterans, Veterans With Other Foreign Service (Germany or Korea), and Veterans With No Foreign Service, and Crude and Adjusted Odds Ratios

| | Vietnam | | Non-Vietnam | | Crude Results | | Multivariate R sults | | | |
| | | | | | | | Model 1[a] | | Model 2[b] | |
Comparison	Rate	No.	Rate	No.	OR	95% CI	OR	95% CI	O	95% CI
Vietnam versus Germany/Korea	158.9	2011	135.6	920	1.2	1.1-1.3	1.2	1.1-1.3	1.	1.1-1.3
Vietnam versus United States service only	158.9	2011	122.6	612	1.4	1.2-1.5	1.3	1.2-1.5	1.3	1.2-1.5

[a] Model 1 contains the primary covariates. No interactions were assessed.
[b] Model 2 contains the primary and secondary covariates. No interactions were assessed.

Table 39. Number of Reported *Infant Deaths,* Crude Rates Per 1000 Live Births Among Vietnam Veterans, Veterans With Other Foreign Service (Germany or Korea), and Veterans With No Foreign Service, and Crude and Adjusted Odds Ratios

Comparison	Vietnam		Non-Vietnam		Crude Results		Multivariate Results			
							Model 1[a]		Model 2[b]	
	Rate	No.	Rate	No.	OR	95% CI	OR	95% CI	OR	95% CI
Vietnam versus Germany/Korea	12.0	152	12.2	83	1.0	0.8-1.3	0.9	0.7-1.2	0.9	0.7-1.2
Vietnam versus United States service only	12.0	152	11.2	56	1.1	0.8-1.5	1.0	0.7-1.4	1.0	0.7-1.5

[a] Model 1 contains the primary covariates. No interactions were assessed.
[b] Model 2 contains the primary and secondary covariates. No interactions were assessed.

elevated serum dioxin levels, and no correlation between average dioxin levels and self-reported exposure to herbicides in Vietnam. Thus, the herbicide exposure index used here may reflect the level of concern and anxiety Vietnam veterans have about the impact of Agent Orange on their health and the health of their children.

If the excess reporting of many different types of child health problems by Vietnam veterans reflects a *real* increase in the occurrence of these conditions, causal factors are not immediately evident. On the one hand, the Vietnam experience can be viewed as a collection of many different "exposures" (*e.g.,* infectious diseases, chemicals, combat), each of which might have been a risk factor for a distinct type of health problem. (However, very little is known about the possible association between paternal risk factors of this sort and reproductive and child health problems.) On the other hand, it is very unlikely that a single chemical or biological factor (such as Agent Orange) would have induced such a heterogeneous array of disorders. We cannot, solely on the basis of the interview data from this component of the VES, fully assess the health of veterans' children. Before we draw any final conclusions, we must consider the findings reported in Part B.

PART B

Birth Records Review Studies

1. INTRODUCTION

In Part B, we describe in detail two special studies that were prompted largely by results of the VES interview data on reported birth defects. Both studies are based on the acquisition and evaluation of hospital birth records of selected veterans' children. For ease of presentation and discussion, we refer to the first study as the General Birth Defects (GBD) Study and to the second, as the Cerebrospinal Malformations (CSM) Study. In part B, we present the background, data collection, analysis, and results of these studies.

1.1 BACKGROUND AND STUDY DEVELOPMENT

In July and August of 1985, we conducted a preliminary analysis of birth defects reported by veterans as part of the VES telephone interview. This initial analysis included 3,718 Vietnam veterans (reporting 6,472 births) and 3,442 non-Vietnam veterans (reporting 5,893 births). We found that the rate of reported birth defects among children of Vietnam veterans was 40% to 50% higher than for children of non-Vietnam veterans. In addition to the reported excess for all birth defects, we observed a difference between the two cohorts for reported neural tube defects and hydrocephalus. As noted in Part A, the final analysis of the interview data shows that the rate of total reported defects remains 32% higher among children fathered by Vietnam veterans.

These preliminary findings prompted discussions among members of the Agent Orange Projects staff about the scientific necessity to verify interview reports of birth defects among veterans' children. We agreed that verification was scientifically necessary and that the concept of verification had been clearly accepted before the data collection phase of the VES began. Consequently, we decided to obtain hospital birth records for a sample of children whose births were reported in the VES interview. To do this, we needed additional information from the veterans about their children and the children's mothers.

As of August 1985, most veterans had already completed the VES interview, but many were still scheduled to receive medical examinations at Lovelace Medical Foundation (LMF). The veterans scheduled to go to LMF provided an easily accessible source for the additional information needed about veterans' children. The alternative was to make telephone call backs to all of the veterans. We therefore decided to obtain the information from the veterans still scheduled to go to LMF.

1.2 STUDY COMPONENTS AND OBJECTIVES

1.2.1 General Birth Defects Study

Beginning January 1, 1986, all veterans attending LMF were asked for information pertaining to the births of all their children and for written consent that allowed CDC to obtain their children's birth records. From January 1 through September 30, 1986, 2,832 veterans attending LMF reported a total of 4,122 children. The eligibility of those children for inclusion in the General Birth Defects Study (GBD) is discussed in Section 2.1.

The GBD Study had two main objectives:

1. To compare the prevalence of total birth defects recorded on hospital birth records in children of Vietnam and non-Vietnam veterans; and

2. To assess the extent of differential reporting between the two cohorts, which would aid in interpreting the interview data.

The first objective is the basis for the primary analysis of the GBD Study: a direct comparison between the two cohorts of all birth defects documented in the hospital records. Because specific birth defects are rare, it is not possible to assess cohort differences for individual birth defects with a study of this size. However, it is possible to compare the prevalence of total defects between the two cohorts. The validity of this analysis relies on the assumption that the quality of hospital birth records and our efforts to acquire them are the same for both cohorts.

The main advantage of this primary comparison of birth defect prevalence rates is that the selection of participants in each cohort was independent of the interview results. Children were not selected into the study on the basis of their reported health status and, consequently, their inclusion is not biased by any differential reporting between cohorts. The potential for misclassification exists in both cohorts—that is, for false-positive reporting ("overreporting") and false-negative reporting ("underreporting"). Because the extent of the two types of misclassification may differ between the two cohorts, an approach that is not affected by these potential misclassifications is desirable.

In a secondary analysis, interview reports were compared with birth records, and measures of misclassification were computed in each cohort. These measures of misclassification aid in interpreting differences between the odds ratios calculated from the interview data and those calculated from the direct comparison of birth records.

In addition to the main objectives, the collection of birth records data enables cohort comparisons for other birth outcomes and perinatal events, such as low birth weight and perinatal mortality, that are regularly noted on these records.

1.2.2 Cerebrospinal Malformations

In addition to the GBD Study, a separate study of reported neural tube defects (NTD) (anencephaly and spina bifida) and hydrocephalus was conducted. Children potentially eligible for the CSM Study were obtained from the original VES interview. Birth records for three types of children were sought for this study:

1. Children with a reported NTD or hydrocephalus, so stated by the veteran in the interview;
2. Children with a reported condition that suggests a probable or possible NTD or hydrocephalus; and
3. All children reported as stillborn.

In this study, we have tried to identify all NTDs and cases of hydrocephalus by focusing on those children most likely to have one of these defects. We took this approach because these defects are very rare (2.5-3.5 per 1,000 births). Consequently, very few of them were expected in the sample of children participating in the GBD Study. Also, these defects are very serious, and it seems likely that a veteran would recall such an event during the interview, if a NTD or hydrocephalus were present in one of his children. The possible exception to this view concerns stillbirths. Conditions in stillbirths are likely to be underreported, and some NTDs are likely to result in stillbirth; therefore, we included all reported stillbirths.

The three types of births listed above represent 386 children reported by veterans in the VES interview. The eligibility of these children for inclusion in the CSM Study is discussed in Section 3.1. Detailed identifying and hospital locating information for these births, along with permission to access the medical records, was obtained by calling the appropriate veterans.

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In the case of stillbirths, we tried to secure the mother's permission to access records (since records of a stillbirth are normally kept in the mother's file). The CDC staff used this information to acquire the birth records from the hospitals (see Section 3).

2. DATA COLLECTION AND ABSTRACTION - GENERAL BIRTH DEFECTS STUDY

2.1 DEFINITION OF STUDY POPULATION

The following eligibility criteria were used to define the final population of children included in the GBD Study:

1. Children reported by veterans attending Lovelace Medical Foundation (LMF from January 1 through September 30, 1986;
2. Live-born or stillborn children;
3. Children conceived after the veteran was assigned to his primary duty location;
4. Children under 18 years of age at the time the records were retrieved; and
5. Biologic children of the veteran.

With the exception of veterans' children who were 18 years of age or older at the time records were retrieved, we determined the eligibility for all potential participants after we had reviewed the hospital birth records. In this way, we could confirm reported dates and events.

Infants reported as stillborn, but weighing less than 500 g (or, if birth weight was not recorded, with a gestational age of less than 22 weeks), were excluded from the study. These early fetal deaths are likely to be underreported by the veterans (they were not asked to report miscarriages at LMF).

To determine if a child was conceived after the veteran was assigned to his primary duty location, we used the child's date of birth from the birth record; however, when a birth record could not be obtained, we used the date of birth from the VES interview or, if this was missing, the date the veteran gave while at LMF. (See Part A, Section 2.4.1, for a complete description of outcomes occurring before military service.)

Children 18 years of age and older are considered to be adults in most States, and their medical records cannot be obtained without their permission. We decided that locating and requesting participation of veterans' adult children was beyond the scope of the present study and, therefore, considered them ineligible.

Of the 4,122 children reported by veterans attending LMF during the period stated above, 381 were conceived before the veterans' primary tours of duty, 41 were 18 years of age or older, 6 were not the biologic children of the veterans, and 11 were miscarriages (not stillbirths). With these ineligible children omitted, the total study population becomes 3,683. In Table 1, the distribution of eligible and ineligible children is shown by the cohort status of their fathers.

2.2 CHILD INFORMATION AND PARENTAL CONSENT

For each child, the LMF interviewer obtained the following information:
1. Child's full name;
2. Date of birth;
3. Name and location of birth hospital;
4. Name and location of transfer hospital;
5. Mother's full name at birth; and
6. Mother's maiden name.

When possible, the information was obtained for all biologic children of the veteran, regardless of whether the veteran is currently or was ever married to the mother. Veterans

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Table 1. Number of Veterans, and Distribution of Eligible and Ineligible Children, by Veteran Cohort Status of Fathers—General Birth Defects Study

	Vietnam	Non-Vietnam
Veterans Attending LMF From 1-1-86 to 9-30-86	1237	1045
All Children Reported at LMF	2150	1972
Ineligible Children		
Child conceived before veteran's primary tour of duty[a]	184	197
Child 18+ years of age	14	27
Veteran not father of child[a]	1	5
Miscarriage[a]	6	5
Final Eligible Study Population	1945	1738

[a] Eligibility was determined after hospital birth record review so that reported dates and events could be confirmed.

were allowed to call home if they needed to verify any information. They signed authorizations to access medical records (Appendix D, Form A) at LMF, unless, of course, they refused to participate in the study. To minimize bias, the LMF interviewers were "blinded" to the military history status of all veterans. Birth information and authorizations to access medical records were sent to CDC biweekly. All records received were reviewed for completeness.

2.3 HOSPITAL RECORD RETRIEVAL

2.3.1 Mail-out Procedures

Letters requesting birth records were mailed to the medical records directors of the hospitals listed on the authorizations received from LMF. A copy of the authorization form and a birth fact sheet that contained identifying information about the child were attached to the letters. (Appendix D, Forms B and C.) We asked each hospital to send a copy of the child's entire medical record covering the birth and associated hospital stay, including (1) discharge summary, (2) birth certificate worksheet, (3) progress notes, (4) diagnostic test results, (5) delivery room record, (6) pathology/autopsy findings and consultations, and (7) physical examination findings.

Mail outs were conducted biweekly, after birth information and authorizations had been received from LMF. An addressed, postage-prepaid, mailing label was enclosed with each request to facilitate the prompt and properly addressed return of requested records. A second request was made if hospitals did not receive the original letter or if the original letter was lost during the medical record search. Several letters were sent in many cases.

2.3.2 Telephone Callback Procedures

Three weeks after the hospital letters were mailed out, telephone calls were made to the hospitals that had not sent the requested records. A specific contact person in the medical records department, usually in the correspondence section, was identified. All subsequent contacts with the hospital were made through this person. During the first telephone call, the contact person was asked to search the hospital files to confirm that the child's record was present and retrievable. Calls to hospitals were repeated every 2 to 3 weeks, until the record

was received or found to be not retrievable. As the targeted date for completing the study drew closer, telephone calls were repeated every 2 to 3 days, and the need for prompt cooperation was stressed.

2.3.3 Transfer Hospitals

Veterans at LMF were asked for the name and location of hospitals to which the child was transferred shortly after birth (transfer hospitals). Mail outs and telephone calls were made to both birth and transfer hospitals on the same schedule. In a few cases, the birth record documented the transfer of a child to a referral hospital, but the veteran did not report the transfer at LMF. In those cases, the veteran was re-contacted to obtain permission to access records from the transfer hospital, and the transfer record was then pursued.

2.3.4 Military Hospitals

Some veterans at LMF reported a military hospital as a child's place of birth or transfer. In these cases, medical records were requested through the U.S. Army and Joint Services Environmental Support Group (ESG) in Washington, D.C. ESG contacted the National Personnel Records Center (NPRC), St. Louis, Missouri, where inactive military records and medical records older than approximately 5 years are stored. Upon receiving a signed consent form from the child's father, NPRC began a search for the requested records. The NPRC sent to CDC written results of all completed searches and the medical records for those searches that were successful. Medical records of children born at military facilities were requested through ESG, regardless of the geographical location of the birth or transfer hospital.

2.3.5 Births Occurring Outside the U.S.

Except for hospitals in Puerto Rico, we did not seek medical records from private hospitals outside the United States. We sought the records from Puerto Rico because many veterans reported that their children were born there. Early attempts by English-speaking CDC employees to obtain the records from Puerto Rico produced minimal results, so a Spanish-speaking member of the CDC staff made the calls. This person also translated some correspondence into Spanish so that records personnel in Puerto Rico could better understand our requests.

2.3.6 Special Problems

During the data collection phase of the study, we encountered several problems that made record retrieval more difficult. In some cases, data received from LMF were incomplete or inaccurate. Authorizations were occasionally scratched out, written over, or, for some children, missing. This necessitated our recontacting the veteran or searching elsewhere for correct data. In some cases, we called several hospitals in the reported birth city to try to locate the correct one. Occasionally, we had to contact State vital records offices to obtain the correct birth information.

In some cases, mothers' authorizations were required to access medical records. Veterans were recontacted to get their permission to obtain the mother's authorization. Hospitals frequently required the mother's authorization to access medical records when the documentation for a stillbirth was with the mother's records. The mother's authorization was also required when the child was given the mother's maiden name in the hospital or when the veteran's name did not appear on the hospital chart. Strict hospital policy sometimes required the mother's authorization for any child.

Once accurate birth information and proper authorizations were obtained, we encountered additional problems in acquiring acceptable birth records from the hospitals. Because of lack of interest and motivation on the part of some medical records personnel, we had to make numerous phone calls and send additional mailings. Unresponsive contact persons at the hospitals were dealt with by asking to speak with a supervisor or a director. Older medical records were often on microfilm and sometimes stored in remote locations. Some records had been sent to outside firms for microfilming and were not returned to the hospitals for as long as 6 months, causing a delay in record retrieval. The receipt of illegible records precipitated additional phone calls and mailings to hospitals. Some records received were for the wrong person or for the wrong admission date, and some were incomplete.

Several births in the GBD Study occurred in hospitals that had been closed at some point during the past 18 years. To determine the location of stored records, we telephoned various agencies, hospital corporations, and State and local health departments. Personnel in privately owned storage areas were difficult to reach by phone, and when reached, were reluctant to cooperate. Numerous letters were sent to these storage locations, and repeated phone calls were made.

State statutes permit certain medical records to be destroyed after a defined period. Record loss was most likely to occur when a stillbirth was documented only on the mother's record and the record had been destroyed as permitted by law. When this occurred, we tried to validate the stillbirth by other means. To confirm the stillbirth, we sought, with some success, birth logs and pathology reports (see Section 2.4.1).

Many hospitals have been consolidated or renamed during the past several years. The renaming or consolidation of a hospital was confirmed by calling any hospital administrator in the city of the child's birth. Administrators were very aware of major hospital changes in their regions, even if the changes did not affect their facilities.

Finally, we needed more time than we expected for mail delivery to the hospitals and to receive the medical records. In some cases, hospitals mailed records that CDC never received. We then made additional telephone or mail requests to the hospitals asking them to re-send the medical record. Occasionally, letters CDC sent to the facilities did not arrive at their destination, again necessitating repeated telephone calls and mailings.

2.4 DATA ABSTRACTION

2.4.1 Ineligible Records

In addition to the eligibility criteria discussed in Section 2.1, additional criteria were applied to the records received before they could be considered "complete" and acceptable. Medical records obtained for live-born infants were abstracted only if the records included a discharge summary or diagnosis, or, at the least, a physical examination by a physician shortly before the infant's discharge from the hospital, documenting the presence or absence of congenital malformations. Generally, a maternal medical record alone was not eligible for abstraction unless it contained a physical assessment of the newborn before discharge. A delivery note alone was not acceptable. Medical records obtained for stillborn infants (and those who died very shortly after birth) were abstracted if (1) the mother's record was available and it clearly documented the outcome of the delivery and the physical assessment of the infant; or (2) other records, such as pathology or autopsy reports for the child, could be obtained. Fewer than 1% of all records received were judged to be inadequate for abstraction.

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Because the veterans were asked if their children were transferred to other hospitals immediately after birth, medical records were obtained from these "transfer" hospitals as well. However, many such records included hospital admissions beyond the newborn period. These records were abstracted only if the hospital admission occurred within 28 days after birth.

2.4.2 Abstraction Form Content

Information abstracted from the medical record included demographic, maternal, obstetric, and infant health data. The record abstraction form is shown in Appendix E. General demographic data included the names of the mother and infant, the mother's address, the hospital name and address, and the types of records sent by the hospital. Maternal information included age at delivery, race, marital status, education, gravidity, parity and number of previous abortions, date of the first day of the last menstrual period, prenatal care, height and prepregnancy weight, weight gain during pregnancy, previous maternal illnesses unrelated to the pregnancy, pregnancy and labor-related complications and illnesses types of labor and delivery, obstetric anesthesia and type of delivery, and the outcome of labor.

Infant health information included sex, plurality, birth weight, gestational age, anthropometric measurements (length, head and chest circumferences), Apgar scores at 1 and 5 minutes, perinatal asphyxia and resuscitation, neonatal conditions (such as jaundice and prematurity), diagnostic procedures, pathology results and surgical procedures, final diagnosis, and other medical conditions and congenital malformations not mentioned in the final diagnosis.

2.4.3 Abstractor Training

Seven abstractors participated in the General Birth Defects Study. During the initial training session, the abstraction form and accompanying instructions were explained in detail and any questions or problems that might arise were addressed. In the pilot training phase, a sample of records was abstracted by each abstractor, including up to five "thick" charts. These were charts of infants with either more than one admission or with medical problems requiring prolonged hospitalization. These charts represented the most difficult records the abstractors were likely to encounter. All records abstracted during the pilot phase were discussed in detail, and problems were solved. Moreover, as part of this initial training period, consistency among abstractors was checked.

After the pilot phase, problems and questions that arose during the course of the study were documented in a special abstraction manual. Decisions and solutions to new problems were documented by abstractors and added to the general guidelines for abstraction in order to minimize inconsistencies among abstractors. Abstractors were "blinded" to the military history status of all veterans.

2.4.4 Coding Abstracted Information

Abstracted information fell into two main categories: (1) specific obstetric and infant variables, such as age, race, type of delivery, and blood group, which were precoded on the abstraction form (Appendix E); and (2) medical conditions and diagnoses and obstetric complications, which were abstracted as open-ended character fields. These conditions were coded according to the International Classification of Diseases, Ninth Revision, (ICD-9) by a trained medical records coder. In coding surgical procedures, the ICD-9 Clinical Modification was used (ICD-9 CM).

2.4.5. Quality Control and Editing Procedures

Editing procedures for the abstracted data included computerized edits for out-of-range values and logic errors. Examples of out-of-range values are nonexistent values for ICD-9 codes and for precoded variables. Examples of logic errors are a date of death that preceded the date of birth and circumcision for a female newborn.

In addition to editing procedures, the quality of the abstraction process was monitored by reabstraction of a sample of records. A 5% random sample of all abstracted records was assigned randomly to abstractors in order to evaluate intraobserver and interobserver agreement with respect to all items obtained from medical records. In addition, all records that showed the presence of one or more congenital malformations in initial abstraction were reabstracted by the same or different abstractors to ensure the validity and reliability of recorded birth defects. The weighting of the reabstraction procedure towards "abnormal" records was purposefully done because of the rarity of birth defects.

Intraobserver and interobserver agreement was assessed by calculating, for each item, the percent agreement between the original abstraction and the reabstraction. Because of the possibility of chance agreement, the *kappa* statistic was computed using the method described by Fleiss (1981). For each variable, the percent agreement and *kappa* statistic were calculated for the random sample reabstraction (N = 184) and the birth defects reabstraction (N = 202). In addition, separate analyses were done for intraabstractor and interabstractor agreement. Results of these analyses are shown in Appendix F (Tables F-1 and F-2).

Table F-1 shows the percent agreement and *kappa* statistic for each item in the random sample reabstraction and birth defects reabstraction. For most variables, agreement is 90% or more and *kappa* is greater than 80% (indicating almost perfect agreement). Generally, percent agreement and *kappa* are somewhat higher for the random sample records than for records with birth defects, which were usually more difficult to abstract.

Table F-2 shows the *kappa* statistic for interabstractor and intraabstractor agreement for both the random sample reabstraction and records with defects reabstraction. Most *kappas* are greater than 80% (almost perfect agreement) or 60% to 80% (substantial agreement). Generally, *kappa* values are somewhat higher for records reabstracted by the same abstractor than for records reabstracted by a different abstractor.

In addition to the quality control procedures described above, all abstracted birth defects were reviewed for accuracy by a physician with expertise in the area of congenital anomalies. All errors and discrepancies were resolved by this individual, and final ICD-9 codes were changed when necessary.

The quality of coding congenital malformations and other medical conditions was monitored by a blind recoding of a random sample of abstracted medical conditions and congenital malformations. Of 50 recoded conditions, 47 (94%) were coded with the identical ICD-9 code and 3 (6%) were not. However, in all three instances, only the fourth digit of the ICD-9 code was different.

3. DATA COLLECTION AND ABSTRACTION — CEREBROSPINAL MALFORMATIONS

Potentially eligible children for the CSM Study were selected from the 24,698 total births reported in the VES telephone interview. Detailed identifying and hospital locating information for these children, along with permission to access medical records, were obtained by calling the appropriate veterans. In the case of stillbirths, an attempt was made to secure the mother's permission to access records (since, as stated earlier, the records of the stillbirth are normally kept in the maternal file). We describe in this section how this information was obtained and used to acquire hospital birth records.

3.1 DEFINITION OF STUDY POPULATION

The following eligibility criteria were used to define the final population of births included in the CSM Study:

1. Children reported by veterans who participated in the VES telephone interview given by Research Triangle Institute (RTI);
2. Children reported as stillborn or with either a clearly stated or possible neural tube defect or hydrocephalus;
3. Biologic children of the veteran;
4. Children under 18 years of age at the time the records were retrieved (if living) and
5. Children conceived after the veteran was assigned to his primary duty location

In the VES interview, veterans reported 403 children as being stillborn, having a neural tube defect or hydrocephalus, or having a condition suggesting a possible neural tube defect or hydrocephalus. Of these, 294 were eligible for inclusion in the final CSM Study population (213 stillbirths and 81 live births). Table 2 shows the distribution of eligible and ineligible children by the cohort status of their fathers.

3.2 LOCATING VETERANS

To obtain birth and hospital information for all children eligible for the CSM Study, members of the CDC staff made telephone calls to the appropriate veterans. This frequently

Table 2. **Distribution of Eligible and Ineligible Children, by Veteran Cohort Status of Fathers — Cerebrospinal Malformations Study**

	Vietnam	Non-Vietnam
Children Reported in VES Interview[a]	216	187
Ineligible Children		
Child conceived before veteran's primary tour of duty[b]	31	27
Miscarriage[b]	31	20
Final Eligible Study Population	154	140
Stillbirths	99[c]	114[c]
Live births	55	26

[a] Children with a reported or probable neural tube defect or hydrocephalus, and reported stillbirths.
[b] Eligibility was determined after hospital birth record review so that reported dates and events could be confirmed.
[c] The number of stillbirths in the CSM Study is less than the number in the interview analysis because infants reported as stillborn, but weighing less than 500 grams (or with gestational age less than 22 weeks), were excluded from this study.

involved relocating the veteran if he had changed his last known address or phone number. In this section, we describe the procedures used to locate veterans whose children were included in this study.

A lead letter explaining the study (Appendix D, Form D) was sent to each veteran at his last known address (obtained at the time of the VES interview). After 7 days, a phone call was made to the phone number where the veteran was previously interviewed. If contact with the veteran was made at this time, an interview was conducted. If the time was not convenient for the veteran, a more convenient calling time was scheduled. Incorrect phone numbers were checked through directory assistance (DA) to obtain a correct phone number.

During the original interview conducted by RTI, veterans were asked for the name, address, and phone number of a friend or relative who would know how to reach them if they moved. If a valid phone number for a veteran could not be obtained from DA, the person the veteran named in the original interview was contacted and asked about the veteran's current location and phone number. All original tracing leads developed by RTI and Equifax were also used in an attempt to recontact the veteran. If the veteran's current phone number or address could not be obtained from any of these sources, a certified, return receipt-requested letter was mailed to the veteran at his last known address. We hoped that the postal service would forward the letter to a more current address and record this address on the green card that was returned to CDC. In the event the certified letter was not acknowledged, a second letter was sent to the same address by regular mail. This letter offered the veteran the opportunity to decline participation in the study. If none of these efforts were successful, the veteran was referred to Equifax for further tracing efforts.

Several veterans were successfully located but could never be reached by phone, because they were either out of town indefinitely or had a job or lifestyle that made it difficult to reach them at home. The previously described locating mechanism was used to try to obtain a correct phone number. Authorization forms and questionnaires were sent to these veterans, with the hope that they would complete and return them, even though verbal contact had never been made.

3.3 INTERVIEWING VETERANS AND MOTHERS OF STUDY CHILDREN

3.3.1 Questionnaire Content
For each child in the study, the interviewer requested the following information from the veteran or the child's mother:

1. Child's full name;
2. Child's date of birth;
3. Name and location of birth hospital;
4. Name and location of transfer hospital;
5. Mother's full name at birth;
6. Mother's maiden name; and
7. Mother's date of birth.

Interviews were conducted with the aid of structured questionnaires. The questionnaire used depended on whether the child was stillborn or live-born and whether the parents were living together at the time of the interview (Appendix D, Forms E and F).

3.3.2 Interviewer Training

Three interviewers were trained for full-time work on this study. Each interviewer was given a notebook with relevant scripts and fact sheets, general procedures for obtaining a complete interview, pertinent letters, and suggested responses to expected questions from veterans and veterans' partners. The interviewers were also instructed on how to deal with initial refusals.

"Dry runs" were made on the telephone and face-to-face between interviewers and between interviewers and other CDC staff members. Interviewing techniques were critiqued and problems were discussed.

3.3.3 Interviewing

The questionnaire, which was limited in scope (see Section 3.3.1), took about 10 minutes to administer. The initial interview was always with the veteran. If the child was stillborn, an attempt was made to also interview the mother.

When possible, current wives or partners of veterans reporting stillborns were interviewed at the time of the initial telephone call to the veteran. Written permission from the veteran was obtained to interview former wives or partners who were the mothers of stillborn children. The current address and phone number of the former wife or partner were also requested. Upon receipt of the written permission, the former wife or partner was contacted by phone and interviewed. An authorization form to access medical records was then mailed to her.

Because most of the children in the CSM study were deceased, the information sought from the veterans and mothers elicited painful memories and made the interview sessions quite sensitive. Thus, veterans hesitated to be interviewed again. To minimize the veterans' and mothers' distress, staff members listened to their concerns and empathized as long as necessary, and this approach often resulted in a successful interview. Many veterans were interested in the purpose of the study and in how they were chosen. These subjects were discussed, and provisions were made to send copies of the published study results to the veterans, if they were requested.

To minimize bias in the interviewing process, staff members were "blinded" to the military history status of all veterans. During the course of the interviews, however, veterans occasionally revealed where they had served.

3.3.4 Refusals

There were several refusals encountered when veterans were contacted for participation in the study. The refusals came from the veterans themselves or from the children's mothers. At the time of the first contact, an effort was made to deal effectively with reluctant veterans, thereby minimizing the chance of an initial refusal. Once a veteran (or mother) refused an interview, a form was completed in which the circumstances surrounding the refusal were stated (Appendix D, Form G). Near the end of the study period, all refusals were reviewed, and those veterans who had not expressed hostility during the initial interview attempt were again contacted in the hope that they would agree to participate.

A few veterans gave complete birth information about their children and agreed to participate, but did not return the authorizations to access medical records. For this group, we had to make numerous return phone calls, re-send authorization forms, and address specific concerns many times. Overnight express letters with express return envelopes were also sent to these veterans to encourage them to return the authorizations.

3.4 HOSPITAL RECORD RETRIEVAL

The hospital record retrieval for the CSM study was conducted in the same manner as for the GBD study (see Section 2.3), with one exception. If a child was reported to have been born alive and to have subsequently died, and if we could not obtain a birth record for the child, we attempted to obtain the child's death certificate. Three children fit this description.

A letter was sent to the appropriate State vital records office requesting a search for the child's death certificate. An attachment to the letter contained the child's last name, first name, date of birth, and place of death, if known. Only one death certificate was received. The other death certificates could not be located, because the information about the children was insuffient.

3.5 RECORD ABSTRACTION

The guidelines and procedures for abstracting records for this study were similar to those for the GBD Study (see Section 2.3). Criteria for ineligibility were identical, except for one minor variation. Since many of the records for this study referred to stillbirths, maternal records were eligible for abstraction. Occasionally, we could obtain only a pathology report or a birth or death certificate, but not a complete medical record. Such records were generally acceptable, if they documented the presence or absence of a birth defect and were from the neonatal period.

4. ANALYTIC METHODS

4.1 HEALTH OUTCOMES

4.1.1 Definition and Classification of Birth Defects

In this study, a birth defect is defined as any structural abnormality present at birth in a live-born or stillborn infant or diagnosed before discharge from the hospital or in a transfer hospital within the first 28 days after birth. We did not consider inborn errors of metabolism and other single gene disorders because their incidence rates are low (most of these conditions have a rate of 1 per 10,000 births or less).

Two broad classes of structural defects were considered in the analyses: (1) "major" or "serious" defects, defined as those that potentially can "affect survival, require substantial medical care, result in marked physical or psychological handicaps, or interfere with a baby's prospects for a productive and fulfilling life" (Erickson *et al.*, 1984a); and (2) "minor" defects defined as those that are not associated with one or more of the above mentioned sequelae.

The distinction between major and minor defects was important for three reasons. First, the ascertainment and recording of minor defects on hospital records can vary considerably among physicians, hospitals, and over time; these defects are generally underascertained at birth. Therefore, underascertainment should be kept in mind in interpreting any findings pertaining to minor defects. Second, because of the impact of major birth defects in terms of morbidity and mortality, it was important to consider these separately in examining risks associated with Vietnam service. Third, since the previous CDC case-control study (Erickson *et al.*, 1984a; 1984b) concentrated on major defects, proper comparison of the results of this study with those of the previous study would require the distinction between major and minor defects.

In classifying birth defects, we adopted the approach of Erickson *et al.*, (1984a) with minor modifications. Under this scheme, we initially used three categories of birth defects: Category I includes those codes that indicate a major or serious defect, Category II includes those codes that do not readily indicate the seriousness of the defect (mostly "other specified anomalies" of a certain organ system), and Category III includes those codes that refer mainly to minor or unspecified defects. A complete listing of codes and conditions under each category is shown in Appendix G.

On the basis of ICD-9 codes alone, all birth defects were initially classified as Category I, II, or III. The medical records for all Category II defects were then individually reviewed and reclassified as either Category I or Category III. Thus, every birth defect is ultimately coded as a Category I or Category III defect, and all analyses are for these two categories.

In ascertaining birth defects from hospital records, we thoroughly reviewed the record. The source of the defect in the record varies: (1) the defect may be listed in the final diagnosis or discharge summary or (2) it may not be mentioned in the final diagnosis, but may be recorded in the physical examination of the newborn, the physician's progress notes, the nurse's notes, the radiologic or pathologic findings, or the surgery or autopsy report. In analyzing the birth defects, we paid special attention to the source of ascertainment.

Finally, we assigned the diagnosis of a defect to one of three levels of certainty. The first level (s = 1) indicates that a physician mentioned the defect without any terms such as "suspected" or "rule out" and that the diagnosis is a "stated defect." The second level (s = 2) indicates defects that a physician suspects, but which were not confirmed on the

medical record (*e.g.*, "rule out congenital hip dislocation"). The third level (s = 3) indicates defects mentioned in a note written by a nurse, but not recorded by a physician. The second and third levels of certainty are collectively labeled here as "suspected" defects.

4.1.2 Cerebrospinal Malformations

In this study, a cerebrospinal malformation is defined as a documented case of anencephaly (ICD-9, 740.0), spina bifida with or without hydrocephalus (ICD-9, 741.0 and 741.9), or congenital hydrocephalus (ICD-9, 742.3). The diagnosis may appear on the birth record, a transfer hospital record, a mother's record (if the infant was stillborn), or any other eligible documentation, such as a death certificate or autopsy report (see Section 3.5 for a discussion of record eligibility).

4.1.3 Other Perinatal Outcomes

The acquisition of birth records afforded us the opportunity to examine the following perinatal outcomes that were not included in the original VES interview:

1. Perinatal mortality, defined in this study as late fetal deaths and early neonatal deaths. All stillbirths that weighed 500 g or more and all infants who died before being discharged from the hospital are included. Separate analyses were done for stillbirths and early neonatal deaths.

2. Low birth weight (LBW), defined as a birth weight under 2,500 g. Birth weight was recorded on virtually all records, but many records did not contain data on gestational age; therefore, low birth weight was analyzed as an outcome regardless of gestational age.

4.2 COVARIATES CONSIDERED IN THE ANALYSIS

In investigating possible associations between place of service and both birth defects and other perinatal outcomes, we evaluated the influence of other variables that are potential confounders or effect modifiers. Several of these covariates that pertain to the veteran have been thoroughly discussed in Part A, Section 2.4.2. For the General Birth Defects Study, we considered these primary and secondary covariates in the analyses of outcomes.

In addition, two new covariates were defined for each child from the birth records. These are maternal age at the birth of the child and gravidity (number of pregnancies). Additional variables (*e.g.* prenatal care, pregnancy complications and illnesses, previous maternal illnesses, maternal weight gain) were considered as potential covariates, but were rejected because data were missing for over 50% of all children.

4.3 ANALYTIC METHODS

Two main analyses of birth defects were conducted: (1) a direct analysis of birth defects, based on hospital records, in which the two cohorts were compared with respect to the rate of birth defects, regardless of interview findings; and (2) a misclassification analysis in which the birth records were compared with the veterans' responses in the interview with respect to the presence and type of birth defects in their children.

In addition, a direct analysis of hospital records was used to compare the two cohorts with respect to perinatal outcomes, including perinatal mortality and low birth weight. No misclassification analysis has been done for perinatal outcomes, because veterans were not questioned about these outcomes during the interview.

4.3.1 Direct Analysis of Hospital Records

In the direct analysis, rates of total defects, "major" defects (Category I), and "minor or unspecified" defects (Category III) were compared between the two cohorts. More detailed analyses include:

1. Analysis of specific birth defects;
2. Separate analyses of birth records only, and birth and transfer hospital records combined; and
3. Separate analyses of birth defects by source of abstracted data (final diagnosis/other) and level of certainty of diagnosis (suspected/confirmed).

Our analysis of specific birth defects is limited by the relatively small number of total births included in this investigation. Consequently, we performed a crude analysis, consisting of a presentation of numbers of cases and crude rates for selected specific birth defects and groups of defects in each cohort. An odds ratio (OR) has been calculated only for those defects or defect groups with 10 or more total cases in both cohorts combined.

For total birth defects, all major defects, and all minor or unspecified defects, two separate analyses were performed. The first analysis relies only on hospital birth records, whereas the second uses both birth records and transfer hospital records as a source of data. If one group of veterans was better able to supply information on transfer hospitalizations than the other, this source of information could be biased. Consequently, a strict definition of a transfer hospital has been used for the analysis: records were included only if the transfer hospital admission occurred within 1 day of discharge from the birth hospital.

In addition, for total defects, major defects, and minor or unspecified defects, separate analyses were performed by the source of the birth defect in the record (final diagnosis only versus anywhere in the record) and by the level of certainty of the diagnosis (suspected versus confirmed). Rates of confirmed defects obtained from the final diagnosis enable an appropriate comparison with previously reported rates of defects that are based on hospital records.

Statistical methods used in the direct analysis of records are similar to those used in the analysis of the interview data (explained in detail in Part A, Section 2.4.3). For each outcome of interest, univariate analyses consisted of comparing the crude rates between children of Vietnam veterans and children of non-Vietnam veterans. ORs were used as the measure of association. Because of the relatively small sample sizes in this study and the rarity of individual outcomes, multivariate adjustment using logistic regression has been done only for total defects, all major defects (Category I), all minor or unspecified defects (Category III), low birth weight, and perinatal mortality.

As discussed in Part A, Section 2.4.3, and Appendix C, the nonindependence of outcomes among siblings of the same veteran did not alter results of the standard logistic regression analysis when compared with results of a modified logistic regression method. Consequently, we have used standard statistical techniques, which assume independent observations, in all analyses of the data.

4.3.2 Misclassification Analysis

In this analysis, our objective was to examine for each child in each cohort the degree of agreement between the interview response and the medical record about the presence or absence of a birth defect. We recognize that the medical record cannot serve as a true "gold standard," because it only refers to the period immediately following birth, whereas the