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3.1.2 Location and Interview Participation Rates

Of the 11,379 mothers eligible for interview, 8,651 (76.0%) were actually contacted and verified to be the mothers of the index babies (Table 9). Of those contacted, 598 refused to be interviewed or were unable to complete an interview because of a language problem (6.9% of those contacted, 5.3% of all eligible). Among those not contacted, 69 (0.6% of all eligible) were deceased, and other relatives (e.g., fathers) gave 161 (1.4% of total eligible) refusals on behalf of the mothers. At the time interviewing ceased, 183 mothers were "ready for interview," but were not contacted. How many of these mothers, with apparently "good" telephone numbers, would have been verified as study mothers is not known. The same general picture applies for fathers, except that a lower proportion were contacted (63.3%), and the refusal rate for those contacted was higher (8.9% of those contacted, 5.7% of all eligible) than for mothers; the rate of refusals that other relatives (e.g., mothers) made for fathers was also higher (6.0%).

Overall, interviews complete to the point of obtaining a military service history for the father were done with either the mother, the father, or both in 74.0% of eligible families; fully complete interviews were done with one or both parents of 73.3% of eligible families (Table 10). As expected, more interviews were completed with mothers than with fathers. Relatively few index babies' fathers were interviewed whose mothers were not interviewed (about 3.5% of the total eligible). Overall, 70.8% of mothers completed an interview containing military history information, as did 57.6% of fathers, and in 54.3% of eligible families both the mother and father completed interviews. About 70% of mothers provided fully complete interviews, as did 56.3% of fathers and 52.9% of mother-father couples. When the study was designed we did not know what level of participation to expect, but for mothers we set a goal of 72% and for fathers, a goal of 80% of the number of mothers' interviews completed. As these figures indicate, the goals were nearly met (Table 10).

The completion rate among Whites was higher than in those parents of Other races (Table 10). For fully completed interviews the percentage of White mothers was 74.7% as compared with 57.7% of mothers of Other races. The contrast was even more striking for fathers: 65.9% for White race fathers versus the much lower 31.7% for Other race fathers.

Among the 11,379 eligible families, 7,133 belonged to the case group and 4,246 belonged to the control group. When the study protocol was written, parents of case group babies were expected to be more willing to undergo the inconvenience of an interview than control group parents because they had had babies with birth defects and presumably would have a particular interest in the study. There was significant concern that it might be difficult to obtain the cooperation of parents of control group babies. Fortunately, this did not prove to be so; indeed, the overall participation rate for control group parents was about 2% higher than for case group parents (Table 10). This is a tribute to the altruism of the control group parents and to the abilities of the study interviewing staff.

Closer examination of participation rates for case and control group parents (Table 10) reveals near equality for those of the White race; none of the contrasts of case-control participation rates for the military history or fully completed interviews for any of the parental categories approaches statistical significance as assessed by chi-square tests for 2 X 2 tables. On the other hand, the participation rate for mothers and fathers of Other race control group index babies is strikingly higher (about 5%), and all of the case-control contrasts are statistically significant ($p < 0.05$). Unfortunately, no data are available that will allow any firm conclusions to be reached about the causes of the better participation in control group parents of Other races. Any analysis for this purpose must, of course, focus on control group parents, and very little data are available for those who did not participate in the interviewing -- just the information derived from birth certificates.

The availability of a father's name may have played a major role in locating the families of study babies. The presence or absence of the name of the father on the birth certificate or on the MACDP case-history form may be an indication of the social circumstances of the parents of an index baby, and those living under poor conditions are more difficult to locate, regardless of the availability of the father's name. The data in Table 11 show that, for both race groups, a strikingly higher percentage of interviews were completed among the mothers of index babies whose certificates or MACDP case-record forms contained their fathers' names. The name of the father was almost always available for White race babies but very frequently was missing for Other race babies (Table 12). For both race groups, fathers' names were more frequently unavailable for case group babies than for control group babies (Table 12). For White race babies, the difference in the proportions is statistically significant ($p<0.05$), but of rather low magnitude (4.1% vs. 2.8% missing, Table 12) and therefore not of much practical consequence. For Other race index babies, however, the difference in proportions of missing fathers' names is not only statistically significant, it is also of a relatively large magnitude (40.5% missing in the case group, 29.1% in the control group, Table 12). This disparity in the proportions of case and control group babies with missing fathers' names, coupled with the lower interview rates where fathers' names were absent, may "explain" much of the difference in the interview completion rates for Other race case and control group parents.

The reasons why fathers' names could be absent from the records used for this study should be discussed. First, about 5% of case babies were stillborn and, for them, fathers' names had to be obtained exclusively from the MACDP case-history forms, a relatively poor source compared with birth certificates. Second, certificates of live birth could not be obtained for all live-born case group babies, and in these cases fathers' names were taken from MACDP forms. On the other hand, certificates were available for all control group index babies. Control group babies were first selected by use of computer tapes of coded certificates, and paper copies of the certificates were requested from the State of Georgia by certificate number. Georgia certificates are filed in such a way that if the numbers are known, the certificates can be easily retrieved. On the other hand, since the numbers of certificates for case group babies were not known, their certificates had to be located through the babies' names. This meant that locating the certificate depended on a great deal of persistence on the part of the personnel doing the search, and even with this effort, the search was sometimes unsuccessful. These two related problems account for a large measure of the difference between White race case and control groups (Table 12), but do not explain a substantial proportion of the difference between Other race case and control groups.

Even in those instances where Other race case group babies' certificates were obtained, fathers' names were more frequently missing than they were on certificates of control group babies. This difference could be the result of sampling variation, despite the low probability value associated with the test of significance. Furthermore, the missing fathers' names could be associated with the birth of a baby with a defect. In the Atlanta area, many Other race group babies are born to unmarried parents. Even under such circumstances, the name of the father often appears on the baby's certificate and MACDP records. But if the baby has a defect, perhaps a father's name is less likely to be placed on the records.

A full explanation of the reasons for the differences in the availability of fathers' names cannot be identified without more data, data that could only be obtained by making a special study of the issue. That being so, it is useful to question how the disparity might affect the inferences to be drawn from the analyses of the study data. As noted above, the difference for the White race group is rather small, and therefore it should cause no more than minimal effects on the analyses. For the Other races group the difference is large enough to be of con-

cern, and the issue will be addressed further in respect to the outcome variables of veteran status and Vietnam veteran status in sections 3.1.3 and 3.1.4.

Table 13 provides another perspective on case/control participation rates by race. Because of the frequency matching on race, about 72% of eligible case and control group parents were White and about 28% were of Other races. For mothers who completed interviews 76.8% were White, but 23.2% were of Other races. For fathers, the contrast is very striking—84.2% of participating fathers were of the White race.

As anticipated, the participation rates were lower for parents of index babies born in the late 1960's and early 1970's and higher for parents of those born in the later study years (Table 14). For mothers of the White race, the participation rates were on the order of 65%-70% for index birth years up to about 1974-1975, after which they were about 80% (Figure 6); for fathers, the rates for the early years were in the low to mid 60% range and in the later years they approached 70%. The two-plateau function instead of a smoother gradient in participation rates from 1968 to 1980 was a surprise. It may be hypothesized that, given a certain battery of tracing tools, the location rates were relatively constant over the years. Recall that for birth years 1974 and on, the mothers' SSN's could be recorded on their babies' birth certificates. Thus part of the explanation of the two plateaus in the early and late year participation rates may be in the location assistance provided by IRS.

For parents of Other races a similar two-plateau function was also found. For mothers the early year level of participation was about 50%, and for the later years it was about 60%; the corresponding levels for fathers were about 30% and 35%, respectively (Table 14, Figure 6). The differences in participation rates for case and control group Other race mothers, mentioned above, vary with the year of the index birth. In general, the differences were most marked for the early study years, but there are some notable exceptions: the case and control group participation rates were quite close in 1968 and 1969, and the rate was substantially higher for controls in 1977. On the other hand, participation rates were higher for control group fathers of Other races in nearly all birth years.

Another perspective on the distribution of study families by year of index birth is presented in Table 15. The data in this table illustrate the frequency matching of case and control group families by year of index birth for those who were eligible for the study. The frequency matching of case and control groups by year of birth was retained among those families from which interviewed mothers derived. These data also show that the distribution of White case group babies remained relatively constant over the index birth years—each year provided 7% to 9% of cases. The picture is different for Other race case group families: the early index birth years provided about 5% of the total and the later years provided 10%-12%. This difference arises from at least two phenomena. First, the numbers of babies of Other races born in the Atlanta area increased markedly during the later study years, and an increase in the numbers of births inevitably led to an increase in the number of babies born with birth defects. Second, the fraction of all babies reported to have been born with birth defects increased somewhat during the later study years. These increases have been most prominent for two heart defects, ventricular septal defect and patent ductus arteriosus, and babies of Other races have been disproportionately affected (Anderson et al., 1978). The cause of the overall rise in the reported rate of defects is unknown. Some part of the rise is probably the result of better recognition and recording in the hospitals, and some part may reflect actual increases in incidence (Layde et al., 1980). Even if these rises are merely the result of better recognition and reporting at hospitals, they should present no problems in drawing inferences about the risk of Vietnam veterans for fathering babies with birth defects. Such a change would only present a problem if the increased reporting were concentrated (or lacking) in Vietnam veterans. And even in the

absence of increased rates of birth defects, a differential reporting for Vietnam veterans would present difficulties.

Participation rates by the third sampling design variable, hospital of birth, are presented in Table 16. White mothers of babies born at six hospitals had participation rates near or above 80% (one of these hospitals, #12, had only very small numbers of case group babies). These hospitals generally serve middle and upper income Whites. White race mothers whose babies were born at hospital #11 had a very low participation rate, about 35%. This hospital is a large municipal hospital that provides service to most mothers in the Atlanta area who are receiving welfare support. The mothers who give birth there are predominantly of the Black race, and the White race mothers who use the hospital are generally from low-income families. The participation rate for White race fathers whose babies were born at hospital #11 was very low—about 22%. This is not surprising, since many of the mothers were unwed at the time they gave birth. More than half of the births to mothers of Other races took place at hospital #11. The participation rate for Other race mothers was lowest among those who had their babies at this hospital (about 51%, Table 16), but it was higher than for White race mothers whose babies were born at hospital #11. Participation rates for mothers of Other races were higher for those whose babies were born at hospitals where the participation rates for White race mothers were high (Table 16).

The frequency matching of control group babies to case group babies on hospital of birth is apparent from the data presented in Table 17, as is the fact that this balance was maintained for mothers who completed interviews.

Participation rates by category and type of defect for mothers and for fathers are given in Table 18 (this table is arranged like Table 1, which presents the numbers of case group babies registered by MACDP), and Table 19 gives completion rates for mothers stratified on race. With few (and relatively unimportant) exceptions, the rates for specific types of defects exhibit the characteristics heretofore presented in this section.

3.1.3 Frequency of Veterans Among Fathers of Index Babies

About 50% of White race fathers were veterans of military service, according to both interviewed mothers and fathers (Table 20). On the other hand, only about 30% of Other race mothers responded that the fathers of their babies were veterans, and roughly 35% of interviewed Other race fathers said that they were veterans. Less than 0.5% of White race mothers did not know if the father was a veteran, whereas 3.3% of Other race case group mothers and 1.8% of Other race control group mothers did not know. There were only small case-control group differences in the frequency of veteran fathers, according to both mothers and fathers who were interviewed (Table 20). For case and control group parents, and for both race groups, the frequency of veteran fathers was about 10% higher in families where both mother and father were interviewed as compared with families in which only the mother was interviewed (Table 21).

We predicted that mothers could provide accurate responses to queries about the veteran status of the index babies' fathers, and the data in Table 22, derived from families in which both mothers and fathers were interviewed, bear out this prediction. These mothers and fathers agreed in 96% to over 98% of families, depending on the particular race and study group (Table 22). There are, of course, no data available related to the accuracy of mothers responses in those instances where no father's interview was obtained, but the high degree of agreement for the families where both parents were interviewed is encouraging. This was taken as evidence sufficient to warrant proceeding with the plan to use the "M" data base for certain aspects of the analysis, as described in section 2.8.3.

The association between the availability of fathers' names on birth certificates and MACDP case-history forms and interview rates was discussed above, with data presented in Tables 11 and 12. Recall that Other race control group parents had higher participation rates than Other race case group parents and that fathers' names were more frequently available for Other race control group index babies than for case group index babies. The association between the availability of fathers' names and veteran status among families with completed mothers' interviews is shown in Table 23. The presence of the father's name in the study records was associated with a higher likelihood that the father was a veteran; this association holds for both race groups and for the case and control groups (Table 23). Recall that the interview rate was higher among those families with fathers' names available at the start of the study (Table 11). Because fathers' names were more frequently available for control group index babies than for case group babies (Table 12), the frequency of veteran fathers among the fathers of control index babies with interviewed parents will be higher than for case group babies. Thus a bias will be introduced into any case/control comparison of the frequency of veterans, but the bias will be small.

As was pointed out before, the magnitude of the difference in the proportions of available names for White race case and control groups is small and of no practical import; therefore, the size of any bias must be negligible. The difference for Other races is larger, and it is worthwhile to consider the potential magnitude of the bias further. According to Other race case group mothers with partially and fully completed interviews, 29.5% of babies' fathers were veterans compared with 30.9% of control group fathers (Table 20). Suppose that the Other race case group had fathers' names available in the same proportion as did the Other race control group. Then one would expect that the reported proportion of veteran fathers would be 30.7%, not very different from the 29.5% observed*. Thus, despite the rather marked difference in the availability of fathers' names for Other race case and control groups, the higher interview rate among control group parents, and the association between the availability of the names and veteran status, the bias that might be introduced is small and of little significance.

As noted before, some mothers and fathers who began interviews did not complete them. Indeed, in anticipation of some parents' desire to quit the interview early, the "premature termination" procedure for obtaining a military history was instituted (see section 2.5.4). There is reason to question if these partially completed interviews are equivalent to fully completed interviews. Respondents who are anxious to stop an interview could agree to "just a few more questions" and then answer them all in the negative to hasten completion.

Insofar as the frequency of veteran fathers is concerned, there are some substantial differences as measured by partially and fully completed interviews (Table 24). Other race mothers who only partially completed an interview more frequently did not know whether the father was a veteran than did mothers who fully completed an interview.

According to control group mothers, the frequency of paternal military service was substantially lower in those instances where the mother only partially completed an interview; no marked difference is apparent among case group mothers (Table 24). A similar pattern of prevalence of veteran status is seen when the responses of fathers with partially and fully completed interviews are compared (Table 24). These data might suggest that the quality of

*Refer to Table 23. Proportion of interviewed Other race control group with fathers' names available = 550/(550+191) = 0.742. Number of Other race case group families with fathers' names available = 0.742 X (746+389) = 842.2, and number with fathers' names not available = (746+389) - 842.2 = 292.8. Expected number of veterans in case group = (0.343 X 842.2)+(0.203 X 292.8) = 348.3; expected proportion of veterans = 348.3/(746+389) = 0.307.

information obtained from partially completed interviews differs from the quality of that gathered from fully completed interviews, at least for control group parents. The data presented in Table 25, however, suggest that this is not so. The data in this table derive from families in which one parent's interview was fully completed and the other's partially completed. For both situations, one in which the mother's interview was fully completed and the father's partially completed and the other in which the father's was fully completed and the mother's partially completed, the agreement of mothers' and fathers' answers was high. Moreover, the frequency of veterans among the control group fathers in both situations was rather low; note also that the parents with partially completed interviews who have contributed to Table 25 represent a sizeable fraction of all parents with partially completed interviews (Table 24). Because of this evidence, the plan to make use of information from partially completed interviews for the "Basic" level of analysis was followed (see section 2.8.3).

Between 50% and 60% of White race fathers whose babies were born 1968 through 1975 were veterans, with the percentage falling in the later study birth years (Table 26, Figure 7). Presumably, this decrease reflects the termination of conscription in July 1973. The pattern for Other race fathers, although less clearly delineated than that for White race fathers, seems to be similar. Substantial variations in the frequency of veterans are to be found among the various hospitals of birth for both White and Other race fathers (Table 27). As for other, previously mentioned characteristics, hospital #11 is notable for having the lowest frequency among the hospitals with reasonably large numbers of births.

It is postulated that the fathers of babies whose mother (or father) was interviewed are more likely to be veterans than the fathers of babies from families in which neither mother nor father was interviewed. This speculation is based on the data presented in Table 28. Interviews began in May 1982 and ceased in October 1983. The fathers of babies whose mothers were interviewed early, and therefore presumably were easier to locate, were more likely to be veterans than the fathers of babies whose mothers were interviewed late in the study data collection phase. If this trend can be extrapolated to the nonparticipants, then one would expect that fathers of babies from nonparticipant families are much less likely to be veterans (the major reason for nonparticipation was inability to locate parents). This should be of no great concern, since no case/control bias is evident in these data—the data presented in Table 28 accurately reflect the frequency of veterans by time of interview for both case and control group parents. Further data on this issue will be presented later.

3.1.4 Frequency of Vietnam Veterans Among Fathers of Index Babies

The frequency characteristics of Vietnam veteran fathers (Tables 29-33) generally parallel the characteristics for all veterans described above. Overall, about 9% to 10% of White race fathers served in Vietnam; for Other races, the figures range from about 6% to 10% according to interviewed mothers and fathers, respectively. The only major characteristic that separates Vietnam veteran fathers from all veteran fathers is year of index birth (Tables 26 and 32, Figures 7 and 8). Very few study fathers whose index babies were born in 1968 were Vietnam veterans, in contrast to 13.4% of White race fathers whose babies were born in 1975 and 10.2% of Other race fathers whose babies were born in 1972. This pattern is what is to be expected, given the time of the Vietnam conflict, the age of the men who served in it, and the usual demographics of fertility.

The fact that there was not a higher proportion of Other race fathers who were Vietnam veterans, as compared with White race fathers, may surprise some readers. It is popularly believed that a disproportionate number of Black men served in Vietnam. We now know, however,

er, that this was not the case, although those Black men who did serve there may have borne a somewhat heavier burden of combat (Veterans Administration, 1980).

A relatively sizable proportion of fathers could not be classified as to Vietnam veteran status (Tables 29-33). Responses that could not be classified include those of "don't know" to the question of whether the father served in the military, served in Southeast Asia, or in Vietnam. They also include insufficient answers to the question of when a father (stated to be a Vietnam veteran) served in Vietnam. To be sufficient, an answer had to provide enough information for us to determine the period of service relative to the date the index baby was conceived (as noted above, in the absence of service dates and if the index baby was conceived after March 28, 1973, a statement that a father was a Vietnam veteran was considered sufficient). Even so, mothers appear to be good substitutes for fathers insofar as their ability to provide a valid answer to the question of whether the father served in Vietnam (Table 31). Thus, the plan to make use of the "M" data base (see section 2.8.3) for certain aspects of the analysis concerning Vietnam veterans was followed. The bias discussed above with respect to veteran status and the availability of fathers' names in the study records applies to Vietnam veteran status. As is the case for veteran status, however, the bias is of negligible magnitude.

As with the frequency of veteran fathers (Table 28), the frequency of Vietnam veteran fathers was related to the time during the study at which the mother's interview was completed (Table 34). In addition to a decrease in the frequency of Vietnam veterans with time to interview, there was a rather striking increase in the proportion of mothers who said that they did not know whether the father was a Vietnam veteran.

3.1.5 Frequency of Vietnam Veterans Among Mothers of Index Babies

This study was designed to determine if male Vietnam veterans are at an increased risk for fathering babies with birth defects. There is also concern that female veterans of the Vietnam war may have an increased risk of having reproductive problems, including having babies with birth defects. There seem to be no unassailable statistics on the number of women who served in Vietnam, but one estimate is between 5,000 and 6,000 (personal communication, Richard Christian, AAOTF, 1984); this is in contrast to the estimated 2.6 million men who served there. The study design used here provides a very powerful approach to the issue for male Vietnam veterans, but because so few women served in Vietnam, this study has virtually no power to detect even a relatively strong effect among women. Indeed, because women Vietnam veterans are a smaller fraction of all women than babies born with many types of birth defects are a fraction of all babies, the usual benefits of case-control studies do not apply. The only way to determine if these women are at an increased risk is to conduct a cohort study, probably including all or most of them. Even if this were done, the study would only be sensitive enough to demonstrate rather large relative risks.

Despite the fact that this study was not capable of detecting increased risks among women Vietnam veterans, interviewed mothers were asked if they had ever been in Vietnam. One mother, the mother of a case baby affected with aortico-pulmonary window, reported that she had served in the Air Force in Vietnam with a combat support group. Another ten mothers said that they had been in Vietnam before the birth of their index babies. Four of these women had been born in Vietnam and had emigrated to the U.S.A. before their babies were born. Two of the ten women had visited Vietnam as airline employees, one mother had been there with the Red Cross, one had "just visited," one had passed through the airport, and the remaining one had been there in connection with the military service of a male relative. Six of the eleven women who had been in Vietnam before their index babies were born were case group mothers and five belonged to

the control group (the overall ratio of case mothers to control mothers with fully completed interviews is 1.6 to 1, Table 10).

3.1.6 Frequency of Self-Reported Exposure to Agent Orange

Fathers' and mothers' answers to the questions about self-perceived paternal exposure to Agent Orange are presented in Table 35. The questions actually posed to parents were phrased in terms of exposure to "herbicides, like Agent Orange" (see questionnaires, Appendix A). Since the emphasis in the questions was on Agent Orange and because the herbicides used in Vietnam are popularly equated as being synonymous with Agent Orange, that term will be used to describe the data in this report.

As noted elsewhere, there is reason to wonder about the ability of Vietnam veteran fathers to provide valid answers to this question and, of course, a mother's answer must derive from her conversations with the father. Furthermore, we thought that answers to this question had a significant potential to suffer from response bias. There is concern that parents of case babies might be inclined to give more affirmative answers because of their natural search for a cause of their child's misfortune. Because of this concern, the study protocol and the analytical plan presented above called for a comparison of the answers to these questions only among case group parents. Further, because there was even greater concern that the mother could not provide accurate answers to questions about paternal exposure, comparisons of the responses to the questions were limited to data derived from fathers' interviews. Nevertheless, it seems important to present distributions of the answers to these questions for mothers as well as fathers and for control group parents as well as case group parents. These data are presented in Table 35, and the responses are categorized into four groups: "yes," "no," "don't know," and "not classified."

For most variables presented in this report, a response of "don't know" can be taken at face value—for example, if a mother said that she did not know whether the father was a veteran, it was assumed that she simply did not know and her response was deleted from all tests of hypotheses. We decided, however, that a "don't know" response to the question about self-perceived exposure to Agent Orange, especially one given by a father, could be of a somewhat different quality than the usual "don't know"—that is to say, "don't know" in this situation could mean something close to "possibly." Therefore, this response has been tabulated separately. The category "not classified" derives from a variety of responses, including those of "don't know" to the questions about veteran or Vietnam veteran status

About 2.5% of responding fathers believe that they were exposed to Agent Orange and the percentage is marginally higher among case group parents. Roughly the same proportions answered that they did not know if they had been exposed. Since roughly 10% of all fathers were Vietnam veterans (Table 30), the data in Table 35 indicate that about 25% of Vietnam veterans believe that they were exposed and that another 25% "don't know," and half believe that they were not exposed. Table 36 presents fathers' responses by year of index birth and generally reflects the distribution of Vietnam veteran fathers by year of index birth (Table 32).

There is a certain internal consistency in the answers given by fathers to the questions about Agent Orange exposure and other questions related to their experiences in Vietnam, experiences that would seem to be related to the likelihood of true exposure. For example, about 90% of fathers who felt that they had been exposed to Agent Orange stated that they had been in areas where the trees had been sprayed to cause leaves to drop (Table 37). On the other hand, only 9% of fathers who said that they had not been exposed claimed to have been in a defoliated area. Moreover, fathers who stated that they did not know whether they had been exposed were less decisive in their answers to the question about having been in a

defoliated area (Table 37). Answers to some questions about place of service in Vietnam (n the jungles, in cities) are also shown in Table 37. The relation between service in the jungle and self-perceived exposure to Agent Orange is similar to, but less striking than, that between exposure and having been in a defoliated area. On the other hand, service in the cities does not distinguish between those who believe that they were exposed and those who believe that they were not (Table 37); similarly, service on bases in the countryside and in other places was not related to self-perceived exposure. This consistency does not imply that the fathers necessarily provided valid answers to the question of Agent Orange exposure, only that their answers were coherent with their answers to presumably related questions.

3.1.7 Agent Orange Exposure Opportunity Indices

The classification of Vietnam veterans on the two exposure opportunity indices are shown in Tables 38 and 39. The distributions are relatively similar for the two, but the index derived from information contained in military records resulted in a slightly higher proportion of men classified in the highest opportunity class. The correspondence of the scoring of individuals on the two indices is presented in Table 40, and as the table shows, 52% received the same score in both systems. Some of the disparity can be attributed to differences in places of service and duties, as stated by the father in the interview and as found in military files. Some of the disparity, however, may result from the fact that the criteria evolved as new situations were encountered during the period that scoring based on information in records was done (see section 2.7); recall, however, that the criteria were stable when scoring based on information derived from interviews was done. Moreover, despite the existence of criteria to guide the AAOTF staff, the process was inherently subjective. Since there are differences in the relative distributions of the two scales, the risks for birth defects were analyzed separately for both indices.

The correlation between the fathers' answers to the question of self-perceived exposure to Agent Orange and their scores on the two indices are presented in Table 41. When fathers who thought that they had been exposed are compared with fathers who thought that they had not been exposed, it is evident that a lower proportion of the former received a score of 1 (lowest level of exposure opportunity). Conversely, a higher proportion of those who thought that they had been exposed received scores of 4 and 5 than did those who thought that they had not been exposed. Thus, there is agreement between the two methods of measuring the likelihood of exposure, but that agreement is far from perfect (Table 41).

The father of a case group baby with "probable" ventricular septal defect had served with the Ranch Hand program in Vietnam during 1962 and 1963; he said that he had "worked on" the aircraft used in the program. Because the rules governing the scoring of Vietnam veterans on the Agent Orange Exposure Opportunity Index (section 2.7) specified exposure to Agent Orange, this man received a score of 1. Agent Orange was not in use at the time of this veteran's service, but the herbicides then in use were probably more heavily contaminated with TCDD than the Agent Orange used later (Young et al., 1978).

3.1.8 Opinion of Parents Regarding the Health of Index Babies

As mentioned above, parents had an opportunity to comment on their perceptions about whether health problems or birth defects were diagnosed in their index babies during the first year of life. This questioning took place during the first part of the interview, when information about a parent's reproductive history was being gathered. Overall, about 14% of case group mothers thought that their index baby had no health problem or birth defect; among White mothers the percentage was 12.9, and among Other race mothers it was 18.6. Table 42

shows that for most types of defects a small percentage of mothers did not believe that their baby had a problem. Two defect groups stand out in that they "contributed" the majority of mothers who said that their babies had no problem: hypospadias and other genital defects, and clubfoot. Other defect categories that contributed substantial numbers of mothers are ventricular septal defect, patent ductus arteriosus, and pyloric stenosis. The first group of defects (hypospadias and other genital defects, and clubfoot) may vary from relatively serious to rather minor, and the parent may not have thought of some of them as a problem or the parent may have forgotten the defect as a problem because it had been corrected. The second group of defects are often not diagnosed before a baby's neonatal hospital discharge and could represent tentative diagnoses made during the neonatal period but not confirmed later in the babies' lives. Furthermore, some mothers may never have been aware that their baby had a defect and some may deny that the baby did. These situations would seem to be most likely to occur along with more readily diagnosed defects in babies who did not survive—cleft lip or anencephaly in a stillborn baby, for example.

We reviewed responses of control group mothers who indicated that their index baby had a problem and identified those problems not classifiable as birth defects by the MACDP (e.g., neonatal jaundice, respiratory distress syndrome). A total of 105 control group index babies remained who were said by their mothers to have defects which, if confirmed and diagnosed during the first year of life, would make the babies eligible for registration by the MACDP (Table 43). Aside from a failure in MACDP registry procedures, there are many reasons why a control index baby could be stated to have had a birth defect. They include a diagnosis made in a doctor's office or in a hospital outside the Atlanta area, a parent's remembering what a physician presented as a possible diagnosis as a diagnosis in fact, or a mother's confusing the index baby with another child during the interview.

The frequency of veteran and Vietnam veteran fathers for case group mothers who did and did not believe that their babies had defects is shown in Table 44. Similar information for control group index babies is presented in Table 45. In the control group there are no differences of consequence between those mothers who said that they thought their index babies were normal and those who said that they thought their babies had birth defects, but there are some differences in the case group that deserve further investigation.

Forty-nine percent of White race case group mothers who said they believed that their index baby had a health problem or birth defect stated that the father was a veteran, as compared with 43% of mothers who thought that their baby was normal (Table 44); this difference is statistically significant ($\chi^2 = 7.42$, $p = 0.006$). A similar and also statistically significant difference is seen for Other race case group mothers. Insofar as the frequency of Vietnam veteran fathers is concerned, no differences are apparent for White race mothers, but there is a seeming difference for Other race mothers (Table 44). This latter difference, however, is not quite statistically significant ($\chi^2 = 3.73$, $p > 0.05$) and will not be considered further.

It seems reasonable to speculate that recognizing (or recalling) some types of defects would take a certain degree of "sophistication" on the mother's part. If this were so, then the difference in the frequency of veteran fathers might be at least partially explained on this basis, since, as will be shown, the mothers of babies with veteran fathers tended to be older and more highly educated than the mothers of babies whose fathers were not veterans. In addition, recall that 12.9% of White race case group mothers believed that their baby had no problem, as compared with 18.6% of Other race mothers, and White race mothers were older and better educated than Other race mothers (see below).

The relationship between maternal age and years of maternal education at the time of the index birth is presented in Table 46. As expected, mothers who had their babies under the age of 20 years had completed fewer years of education than mothers who had their babies at older ages. Women who had their babies between the ages of 30 and 34 years were the most highly educated. The patterns for White and Other race mothers were similar, although the Other race mothers generally tended to be younger and less well educated than White race mothers (Table 46).

For both White and Other race groups, the fathers of babies born to young mothers were less frequently veterans than fathers of babies born to older mothers (Table 47). For both race groups, the fathers of babies born to the less well-educated mothers were also less frequently veterans (Table 48). (All of the differential data patterns presented in Tables 46-48 are statistically significant, $p < 0.05$, according to chi-square tests for the various R :: C tables.)

The associations between maternal age and mothers' opinions about the health of the case group index babies and between maternal education and opinions are presented in Table 49; for the sake of simplicity only White race mothers are represented, but the same patterns are found for Other race mothers. Significantly more young mothers believed that their index babies had no problems than did older mothers (heterogeneity $\chi^2 = 9.18$, $p > 0.05$; extended Mantel-Haenszel test for trend in proportions $\chi^2 = 8.38$, $p = 0.004$). In addition, a somewhat higher (but not statistically significant) percentage of the more highly educated mothers acknowledged that their baby had a problem than did the less well educated (Table 49; heterogeneity $\chi^2 = 2.91$, $p > 0.05$; extended Mantel-Haenszel test $\chi^2 = 2.91$, $p > 0.05$).

The associations between maternal age and education and the mothers' opinions about the health of the index babies and between these variables and fathers' veteran status do not fully explain the association between the mothers' opinions and veteran status; however, they do account for some of it. An excerpt of the relevant data is presented in Tables 50 and 51. For mothers of all ages (except 20-24 years), fewer fathers of babies thought not to have birth defects were veterans; the most striking difference was for mothers aged 25-29 (Table 50). The crude odds ratio for the data in the total lines of Table 50 (i.e., the odds of a veteran father, given that the mother thought that the baby had a defect, relative to the odds of a veteran father, given that the mother thought the baby had no defect) is 1.31 ($\chi^2 = 7.63$, $p = 0.006$), but the odds ratio adjusted for age is 1.23 ($\chi^2 = 4.24$, $p = 0.039$). Thus, adjustment for differences in the age distributions of those mothers who did and did not believe that their baby had a defect seems to reduce the effect, but hardly removes it completely. The age group 25-29 is further considered in Table 51, which shows the same effect for all education categories while age is held constant. An overall analysis of this deficit of veteran fathers among those whose babies were thought not to have a birth defect was done by using the Mantel-Haenszel test, with stratification of the data by age and education. For Whites the result was virtually identical to the result described above, where stratification of the data was limited to maternal age alone; a similar result obtained for Other race mothers. In summary, some data support the notion that education and age may partially explain the fact that some mothers believe that their index babies had no defects, but they do not fully explain the differences in the frequency of veteran fathers associated with those opinions.

If it is postulated that some of the deficit of veteran fathers among mothers who did not believe that their babies had a problem is due to a lack of a certain degree of "sophistication," then it is not surprising that age and education do not explain more of the effect—these variables can only be expected to imperfectly measure this "sophistication."

Whatever might explain the differential frequencies of veteran fathers just described, it is without doubt that the opinions of some of the mothers are valid and some are invalid. Unfortunately, there is no simple method that can be used to determine, in specific instances, whether the MACDP case/control designation or the mother's opinion is in error. In trying to estimate the effect of these disagreements on the analyses, one can explore two extreme possiblities. First, it can be assumed that the mothers' opinions are in all instances correct, and second, it can be assumed that all MACDP case/control designators are correct. Whatever extreme possibility is considered, the deletion of control group mothers who feel that their baby had a defect would have little effect on the analyses, since they constitute only a small fraction of all controls and since there is little, if any, difference in the frequency of veterans among the fathers of babies whose mothers did and did not believe their baby had a defect. The situation for case group families is less straightforward.

On the presumption that the MACDP case definition is invariably correct, all case group mothers should be retained in the analyses, no matter what their opinions. Keeping the case mothers who felt that their index babies had no defect in the analysis would tend to lower the frequency of veteran fathers in the case group as a whole. This would have the effect of increasing the chances of finding a significant difference between cases and controls in the frequency of veteran fathers. As a consequence, there would be an increased likelihood that the comparison group for tests of hypotheses regarding Vietnam veterans (and the Agent Orange exposure variables) would be limited to non-Vietnam veterans (see section 2.8.3). On the presumption that the opinions of mothers are most frequently correct, such a limitation might be inappropriate, since restricting comparison groups for tests regarding the risks of Vietnam veterans would result in a smaller sample size, with consequently reduced power.

Therefore, on balance, it seemed most appropriate to perform the bulk of the data analysis by using the predefined case and control definitions: registry by the MACDP for cases and no registry for controls. A few of the major analyses, however, were repeated, with the case and control group families deleted when the study records and the mothers' opinions were at variance. These additional analyses were done for all defects combined and for the specific defect types that account for most of the disagreements. Moreover, the additional analyses were limited to the "Basic" level of analysis, with the modification that parents with partially completed interviews were excluded. In the usual "Basic" analyses, parents with partially completed interviews were included to maximize the numbers available. But to know a parent's opinion about the health of the index baby, one must have a completed first interview, and that opinion would not be known for many parents with partially completed interviews. If the exclusion of case and control group families where the mother's opinion is at variance with the MACDP classification in the "Basic" phase did not change the results, as was expected, then there seemed to be little reason for carrying this exclusion forward to the other analytical phases.

So far, no data have been presented regarding interviewed fathers' opinions about the health of their index babies. These data have not been tabulated because we decided that the babies' mothers' opinions are to be preferred to the fathers'. Recall that the analytical plan called for use of the "M" or "MF" data bases in all analyses except the "Basic" phase for the Agent Orange-related exposure variables (see section 2.8.3; Figure 5). Thus, the mothers' opinions will be available for all analyses except for those where the consideration of parental opinion is precluded by the desire to include partially completed interviews (see paragraph above).

3.2 TESTS OF HYPOTHESES

The results of the major analyses prescribed in the Analytical Plan (section 2.8.3) are presented in this section, arranged hierarchically along the axes of the analytical matrix (Figure 5): first, results of analyses at the Basic level of the Adjustment axis; second, analyses at the Primary Adjusted level; and third, at the Secondary Adjusted level. Within each of these levels of the Adjustment axis, the 96 defect groupings will be considered, and within each of the defect groupings the tests of the hypotheses defined on the Hypothesis axis (Figure 5) will be described.

3.2.1 Basic Analyses

The results of the analyses at the Basic level of the Adjustment axis are presented in Table 52. This is an extensive and complicated table, and a general description of its organization is in order (readers who wish to know the details of the various logistic regression models used and how the variables were coded may refer to Appendix B). As just noted, the table is arranged by the defect groupings selected for this report and presented in Table 7. For each defect group, the four hypotheses specified in section 2.8 are evaluated. The first hypothesis to be evaluated is that veterans of military service have a different risk of fathering babies with birth defects than other men. As specified in section 2.8, the data used to test this hypothesis exclude veterans who are defined as Vietnam veterans. The purpose of this test is to determine the need for limiting the data, for the tests of the remaining three hypotheses, to families in which the father was a veteran. The second hypothesis to be evaluated, for each of the defect groups, is the major focus of this study: do Vietnam veterans have a different risk for fathering babies with birth defects than other men (or other veterans, if the data are limited to veterans as a result of the test of the first hypothesis)?

The third hypothesis to be evaluated is whether the risk of fathering babies with birth defects increases (or decreases) with increasing scores of the Agent Orange Exposure Opportunity Index. As described above, two index scorings were done for each Vietnam veteran, and there was a substantial lack of correspondence between the two scores. Therefore, there are two tests of this hypothesis: one is done with the index based on data about veterans obtained from military records and the other is done with the index based on information obtained from the veterans during the interviews. The index scores were treated as continuous variables in the logistic regression analyses. For these analyses, men who were not Vietnam veterans were given a score of 0, and Vietnam veterans scored on the indices were given a value between 1 and 5 (see Tables 38,39).

The fourth and last hypothesis to be evaluated is whether self-reports of exposure to Agent Orange are associated with the occurrence of defects. As noted earlier, an answer of "don't know" to the question about Agent Orange exposure is considered to have a special quality that sets it apart from an answer of "don't know" to most other questions posed to parents. Therefore, the association between the self-reports of Agent Orange exposure and the occurrence of defects is evaluated twice. The first evaluation is the contrast between those men who said "yes" to the question and those who said "no" (men who were not asked the question because they had not been in Vietnam before their index baby was conceived are included with the men who answered "no" to the question). In the second evaluation of the hypothesis, those fathers whose response was "don't know" were combined with those who answered the question in the affirmative.

Except for the Veteran Status hypothesis, the test of each hypothesis includes evaluations for interactive effects of two of the sampling design variables, race and period of birth. That is to say, the possibilities that the risks for fathering babies with birth defects differ between

the races and between the periods of birth were assessed. If statistically significant ($p<0.05$) interaction (i.e., effect modification) was found, separate displays are given for tests of the hypothesis stratified by race, period, or both, as appropriate.

As noted in Figure 5, the "M" data base (i.e., all mothers' interviews) is used to test the first two hypotheses at the Basic level of the Adjustment axis, and the "F" data base (i.e., all fathers' interviews) is used to test the last two hypotheses. In testing all hypotheses at the Basic adjustment level, data derived from partially completed interviews as well as from fully completed interviews are used.

For each hypothesis, the number of responding parents is displayed by case/control group status and "exposure" status. The definition of the control group varies with the hypothesis under consideration. For the first three hypotheses, the control group comprises the families of index babies born without defects. For the fourth hypothesis, concerning the effect of self-reported Agent Orange exposure, the control group comprises families of babies born with all types of defects except the defect under consideration; the families of babies born without defects are not included.

The meaning of the term "Exposure Status" also varies with the hypothesis under consideration. For the test of the risk of veterans, "exposure" ("+") signifies veterans (excluding Vietnam veterans), whereas no "exposure" ("−") signifies nonveterans; similar definitions of "exposure" apply to the tests of hypotheses concerning Vietnam veterans and self-reports of Agent Orange exposure. For the tests of the hypotheses about the risks associated with the Exposure Opportunity Indices, "exposure" ("+") signifies Vietnam veterans who received any index score and no "exposure" signifies men who were not scored on the index. Thus, those represented by a "+" had a score of between 1 and 5 (Tables 38,39), and those represented by a "−" had a score of 0, for purposes of the logistic regression analyses.

A conditional logistic regression derived odds ratio or coefficient ("beta") is presented for each hypothesis, along with 95% confidence limits for the odds ratio or beta. For the hypotheses regarding veterans' risks, Vietnam veterans' risks, and risks associated with self-reports of Agent Orange exposure, an odds ratio is presented, whereas a beta is presented for the tests concerning the association of birth defects risks and the Agent Orange Exposure Opportunity Indices. The odds ratios that are significantly different from 1.0 (i.e., with 95% confidence limits which do not overlap 1.0) are highlighted by an underlining of the confidence limits. An odds ratio that is not significantly different from 1.0 is taken to indicate that there is no evidence to support the position that those "exposed" have a different risk from those "not exposed" for fathering babies with the particular defect under consideration; an odds ratio significantly greater than 1.0 is an indication that "exposed" fathers have a higher risk than those "not exposed," and an odds ratio significantly less than 1.0 indicates that the "exposed" are at lower risk.

Statistically significant betas (i.e., those whose 95% confidence limits do not include 0.0) for the tests of hypotheses concerning the Agent Orange Exposure Opportunity Indices are also highlighted by underlining. A significant beta implies that there is a monotonic trend in risk as the value of the exposure index increases; if the beta is positive, the risk increases with increasing index scores, and if the beta is negative, the risk decreases with increasing index scores. A nonsignificant beta implies that there is no evidence in the data at hand that will support the position that there is a monotonic trend in risks; an exponential relationship between the odds of fathering babies with birth defects and the index is implied by the use of logistic regression.

Findings of significant odds ratios or betas cannot be considered in isolation. They are but one feature of the data considered in the inferential process used to arrive at conclusions

about the hypotheses being considered. Many other factors must be considered in making inferences. The magnitude of an estimated risk, its consistency with other relevant facts drawn from within and from outside the study, the possible effects of various biases, and so on, must also be factored into the judgmental process. This should be kept in mind as the results of the tests of the hypotheses are described.

The number of cases that contribute to the analyses for a particular defect group depends on the hypothesis being tested. The number of controls that contribute is related to the particular hospital-of-birth/period-of-birth/race distribution of the cases contributing. The data were stratified on the sampling design variables, and controls were excluded if they belonged to strata from which no cases were drawn. This exclusion is of no concern, since for all defect groups (save for the composite group comprising all case babies) the contributing controls substantially outnumber the cases. The control-to-case ratio is generally so high that almost no gain in statistical power would be obtained by using all controls, and the validity of the results might suffer if they were used (all controls could be used by not stratifying on the sampling design variables).

The features of Table 52 can be described concretely by referring to the first page of the table where the data for the defects group "All Case Babies" and "Multiple Defects" are found. For the test of the first hypothesis, whether veterans have a different risk than other men for the group "All Case Babies," there were 1,659 fathers of case group babies and 1,047 fathers of control group babies who were veterans, and 2,727 case group fathers were nonveterans, as were 1,652 control group fathers; Vietnam veterans were excluded from this analysis. The logistic regression-derived odds ratio is 0.94. The 95% confidence limits on this odds ratio are 0.85 to 1.04, indicating that the ratio of 0.94 is not significantly different from 1.0. Thus, we may conclude that there is no evidence in these data to support the position that veterans (excluding Vietnam veterans) have a risk different from other men. If the confidence limits had not included 1.0, we would have concluded that the odds ratio of 0.94 indicated a lower risk among veteran fathers. Since there is no such evidence, the tests of the remaining hypotheses for this defect group will include data obtained from families with nonveteran fathers as well as those with veteran fathers.

There were 428 case group fathers who were Vietnam veterans and 268 Vietnam veterans who were control group fathers. The odds ratio for the test of the hypothesis that Vietnam veterans have a different risk for fathering babies with birth defects is 0.97, with confidence limits of 0.83 to 1.14. Thus, there is no evidence that Vietnam veterans, in general, have a greater aggregate risk of fathering babies with all types of major birth defects.

Three hundred and nineteen case group fathers received Agent Orange Exposure Opportunity Index scores for the index constructed from military records information, as did 1,179 control group fathers; the distributions of the index scores for this and all other defect groups are presented in Appendix C. The beta for a test for a trend in odds ratios related to the index scores was 0.03, with confidence limits of -0.04 to 0.10. Since the confidence limits include zero, we may conclude that these data provide no evidence to support the notion that greater opportunities for Agent Orange exposure are associated with higher risks of fathering babies with birth defects. A similar conclusion follows from an examination of the data derived from the Exposure Opportunity Index constructed from information provided by Vietnam veterans during the interviews.

For the composite "All Case Babies" group, the hypothesis regarding the possible association between self-reported exposure and risk is not tested. As specified in the study protocol, and as reiterated in section 2.8.3 of this report, data derived from the fathers of normal control babies were not used because of the fear of response bias. Instead, the protocol called for

a comparison of the frequency of affirmative responses among the fathers of babies with one particular defect with the frequency of affirmative responses among the fathers of babies with all other types of defects. Since the group "All Case Babies" comprises just that, no reference group is available. For all of the remaining defect groupings, however, an appropriate reference group is available.

As found for all types of defects combined, there is no evidence that veterans, or Vietnam veterans in general, or Vietnam veterans who had the higher Agent Orange Exposure Opportunity Index scores had a different risk for fathering babies with "Multiple Defects." Because all case babies were not born with multiple defects, the fourth hypothesis can be tested—that is, the hypothesis that Agent Orange exposure, as measured by self-reports of the fathers, is associated with different risks of fathering babies with multiple defects. Twenty-five fathers of babies born with multiple defects and 83 fathers of babies born with "single" defects stated that they had been exposed to Agent Orange. The logistic regression-derived odds ratio estimate is 1.07, with confidence limits of 0.67 to 1.70. A similar pattern is seen for the test of this hypothesis in which responses of "don't know" to the question of Agent Orange exposure are combined with the "yes" responses ("Self-Report AO Exposure 2"). Therefore, we may conclude that these data give no support to the position that self-reported exposure to Agent Orange is associated with increased (or decreased) risks of fathering babies with multiple defects.

These patterns of no different risks for veterans, Vietnam veterans, those men who reported that they were exposed to Agent Orange, and those Vietnam veterans who had the higher Agent Orange Exposure Opportunity Index scores for all defects combined and for multiple defects are generally repeated for the remainder of the defect groups. The following comments on the Basic level of analysis will be restricted to the exceptions to this general rule.

Veterans (excluding Vietnam veterans) had a significantly lower risk for fathering babies with all types of sex organ defects (see "Total Sex Organ Defects," Table 52). Because veterans had a significantly different risk for these defects, the remaining three hypotheses were tested by using only data gathered from families in which the father was a veteran. None of the tests of hypotheses connected with service in Vietnam were significant.

The estimated risks for fathering babies with spina bifida are higher for men with the higher scores on the Agent Orange Exposure Opportunity Indices—the betas for both of the indices are positive, and their confidence limits do not include zero.

Veterans had significantly lower estimated risks than other men for fathering babies with hydrocephalus and anophthalmos. Men who had the higher scores on the Agent Orange Exposure Opportunity Index derived from interview-obtained information had higher risks for fathering babies with coloboma, as did those men who thought they had been (or might have been) exposed to Agent Orange.

Vietnam veterans' risks for fathering babies with ventricular septal defect varied significantly over the three birth periods, but in no single period was the risk significantly different from 1; the highest risk period was January 1968 through April 1972. The same pattern is repeated for the Agent Orange Exposure Opportunity Index based on information derived from interview-provided information and for the second test of the hypothesis that self-reports of Agent Orange exposure are associated with different risks. A very similar pattern is observed for "selected" ventricular septal defect ("selected" means that "possible" and "probable" diagnoses have been excluded, see Table 7), except that the risk for Vietnam veterans and those who said that they had been or might have been exposed to Agent Orange was significantly higher than 1.0 for the first birth period.

Risks associated with the second Agent Orange Exposure Opportunity Index for patent ductus arteriosus varied significantly over birth periods, with the risk during the last period decreasing significantly with increasing opportunities for exposure. A similar pattern is seen for "selected" patent ductus arteriosus, except that the inverse association between the index scores and risk in the third period does not quite reach statistical significance.

Cleft palate risks associated with the second Agent Orange Exposure Opportunity Index varied significantly over birth periods, but in no single period was the risk significantly different from 1.0.

Veterans had a significantly higher risk for fathering babies with cleft lip with or without cleft palate; Vietnam veterans who received higher scores on the second Agent Orange Exposure Opportunity Index had a higher risk for having babies with this type of defect.

Other race Vietnam veterans had a higher risk for fathering babies with pyloric stenosis, but no association between the risks and the Agent Orange exposure measures was noted. There was a race-specific variation in Vietnam veterans' risks for fathering babies with anomalies of intestinal fixation, but neither of the individual risks were significant. Veterans had a significantly lower risk of fathering babies with defects of the liver and biliary system.

No significant tests of hypotheses are found for the category "Clubfoot," but there is race interaction for Vietnam veterans for "Selected Clubfoot" ("selected" indicates that cases with "possible" and "probable" clubfoot diagnoses and with metatarsus adductus have been excluded, see Table 7).

Vietnam veterans have a significantly higher estimated risk of being the fathers of babies born with "Specified Anomalies of the Nails." This defect rubric includes hypoplastic nails, absent nails, and hyperconvex nails. The father of a baby with a defect classified as edema of the legs was a Vietnam veteran whose response to the question of Agent Orange exposure was classed as "don't know." This resulted in a statistically significant test for the second evaluation of the self-reported exposure hypothesis.

The two Vietnam veterans who fathered babies with situs inversus received higher scores on the two Agent Orange Exposure Opportunity Indices than Vietnam veteran fathers of control group babies.

Veterans had a significantly lower risk of fathering babies with "Other Specified Syndromes."

Finally, there was a significant positive association between the level of Agent Orange exposure opportunities as determined from information obtained during the fathers' interviews for the category "Other Neoplasms." The confidence limits for the risk for Vietnam veterans in general just barely include 1.0 (limits 0.99-3.29). The congenital neoplasms included in this group are dermoid and epidermoid cysts (26 cases), teratomas (14 cases), lipomas (9 cases), harmartomas (5 cases), central nervous system tumors (5 cases), Wilms tumors (3 cases), neuroblastomas (3 cases), hepatoblastoma (1 case), rhabdomyosarcoma (1 case), and miscellaneous benign tumors (24 cases).

A very large number of statistical tests were performed for the Basic level of analysis. For the evaluation of a particular hypothesis (except for the Veteran Status hypothesis) for a specific defect group, six tests were done, one for the overall hypothesis, four for interactions on period of birth, and one for interaction on race. For the Veteran Status hypothesis, only an overall evaluation was done. For each defect six hypotheses were evaluated, if the two Exposure Opportunity Indices and the two self-reports of Agent Orange exposure are counted separately. Thus, for this level of analysis alone, 2,976 (96 x 5 x 6 + 96) tests of significance were done. If all of these tests were independent and if, in fact, there were no relationship between the "exposures" and the defects, we would expect about 149 to be statistically signifi-

cant at the alpha level used, 0.05. In all, 31 significant tests were observed. But many of the tests cannot be considered independent tests of significance, and the true expected number significant at the alpha = 0.05 level is unknown. Dependence of the various tests occurs for at least four reasons. First, several of the defect groups are aggregate groups formed from a combination of other groups that are subjected to separate analytical scrutiny. Second, certain defect types often occur in association with other defects, as, for example, several cardiac defects occurring in the same baby, or for another example, the well-known combination of Down's Disease and certain cardiovascular defects. Third, the four tests made for interaction on period of birth are clearly dependent. For example, an extreme value in one period would probably show significant interaction with both other periods. Fourth, the two tests done for the Agent Orange Exposure Opportunity Indices and the two tests made for self-reports of Agent Orange exposure are highly dependent. Neither of the tests done for these two hypotheses can be considered truly independent of each other, nor can any of them be construed to be independent of the test for an overall association with Vietnam veteran status.

Ignoring the tests made for interactions on period of birth and race, results of the significant tests can be summarized as follows: veterans had significantly lower risks for four defect groups (or three, if the significantly lower risks for all sex organ defects and for hypospadias are counted only once) and a significantly higher risk for one group. This is fairly close to expectation at our alpha level (assuming independent tests), since tests for 96 defect groups were done. Vietnam veterans had a significantly higher risk for only one defect group, somewhat lower than expected. Results of several tests on the Exposure Opportunity Indices and on the self-reports of Agent Orange exposure were statistically significant. Although these tests are not excessive in number (assuming test independence), the results for all tended to be in the positive direction.

Four Basic level analyses were repeated after removal of the case and control group families in which the mother's opinion of the index baby's health was at variance with the study definition. The four defect groupings for which the analyses were repeated were All Case Babies, Total Sex Organ Defects, Hypospadias, and Selected Clubfoot. The latter two defect groups contribute a majority of the families in which the mother's opinion was at variance with the study definition. For the All Case Babies group, there was essentially no change in the results, although the point estimates of the odds ratios for the Veteran and Vietnam veteran hypotheses were slightly closer to 1.0 than they were for the analysis that included all families. For the Total Sex Organ Defects group, the odds ratio for the Veteran hypothesis moved closer to, and was not significantly different from, 1.0; in addition, there was no significant variation over periods of birth as there was when all families were included. For Hypospadias, the results were nearly identical with those obtained when all families were included, although the point estimate of the odds ratio for the Veteran hypothesis was closer to 1.0. Last, the results for Selected Clubfoot were virtually identical in the original and repeat analyses. None of these findings indicate that further work with this issue is needed.

As mentioned earlier, the father of a case group index baby with "probable" ventricular septal defect had received a score of 1 on the two Agent Orange Exposure Opportunity Indices. Since the herbicides to which he was probably exposed during 1962 and 1963 were relatively heavily contaminated with TCDD, certain relevant Basic analyses have been repeated. These analyses were of the two Exposure Opportunity Indices for the following defect groupings: All Case Babies, Total Cardiovascular Defects, and Ventricular Septal Defect. For these special analyses, this father was given index scores of 5. The logistic regression-derived betas from these analyses are virtually identical to those presented in Table 52.

3.2.2 Primary Adjusted Analyses

The Primary Adjusted analyses, in which the results are adjusted for possible confounding by the "essential" covariables, are presented in this section.

The "essential" covariables, identified by the "nominal group" described in section 2.3.3, are 1) age of the mother at the time of the index birth, 2) mother's education at the time of birth, 3) mother's alcohol consumption during the 4-month period from 1 month before conception through the first trimester of pregnancy, and 4) birth defects in the index babies' first-degree relatives.

The Primary Adjusted analysis was done twice, once with the families having mothers, fathers, and siblings (born before the index baby) who had birth defects excluded and once with these families included. In both sets of analyses, the logistic regressions were done in such a way that stratification on the three sampling design variables was preserved.

Two logistic regressions were done for each hypothesis for each defect group: one in which the risk for fathering babies with defects was merely adjusted for the possible confounding effects of the "essential" covariables, and another in which the possibility that there is interaction between the risk and the covariables was assessed (the tests of interaction on period of birth and race done in the Basic analysis were not repeated).

The results of both sets of Primary Adjusted logistic regressions were generally similar to those found at the Basic level of analysis, indicating that the four covariables were not important confounders with respect to most of the hypotheses being tested. Because of the similarity of the results of the Basic and Primary Adjusted analyses, no full presentation of results of the Primary Adjusted analyses will be made. Table 53 shows the results for the first 14 defect groups only (i.e., the groups comprising the various aggregates of ICD-8 codes); these data derive from the regressions that included the families with first-degree relatives affected with birth defects. The only major difference in the results of the Basic analyses and the Primary Adjusted analyses was for the group Complex Cardiovascular Defects. In the Basic analysis, the relative risk for Vietnam veterans was not significantly different from 1.0, but the point estimate was less than 1.0 (Table 52). In the Primary Adjusted analysis, the risk for Vietnam veterans was significantly lower than the risk for other men (Table 53).

For some defect groups, the "essential" variables were shown to be significantly related to the occurrence of the defects. That is, a covariable, say maternal age, was shown to be significantly related to the occurrence of the defect, once the other variables under consideration are taken into account. And, of course, a few of the tests for interactions were found to be significant, but none were considered to be of enough concern to warrant further analysis. The associations between the three covariables and the risks of defect occurrence are briefly described below.

For one or more of the hypotheses tested, mother's age was significantly and positively related to the occurrence of the following defects: complex cardiovascular defects, endocardial cushion defects, heart valve anomalies, pancreas anomalies, ovarian anomalies, endocrine anomalies, Down's Disease, and several others. Mother's age was significantly and negatively related to microcephalus, common truncus arteriosus, cleft palate, vaginal anomalies, omphalocele, gastroschisis, and other defects.

Similarly, for one or more of the hypotheses tested, mother's education was significantly and positively related to the risk for the group "Other Neoplasm"; in other words, the risk for congenital neoplasm was greater for more highly educated women. Education was also positively related to the occurrence of complex heart defects, ventricular septal defect, and pyloric stenosis. Education was significantly and negatively related to the occurrence of these

defects: anencephalus and spina bifida, hydrocephalus, buphthalmos, congenital cataract, ear anomalies, choanal atresia, and several others.

For several defect groups, mother's alcohol consumption was significantly and positively associated with the risk of defects occurring in their babies; no significant negative associations were found. For one or more of the hypotheses tested, alcohol consumption was related to defects in the following groups: tracheo-esophageal stenosis and atresia, atresia and stenosis of the small intestine, several types of kidney defects, and diaphragmatic hernia.

The hypothesis that Vietnam veterans (and/or those who may have been exposed to Agent Orange) have a different risk of fathering several affected babies is evaluated with the data presented in Tables 54 and 55. The data in these tables derive from case group families only and pertain only to full siblings of the index babies (i.e., siblings born to the same mother and father as the index baby); the data are further limited to those derived from siblings born after the index baby. This data limitation should make it possible to evaluate the hypothesis free of the possible confounding effects of preexisting risks. First, it can be seen that veterans (excluding Vietnam veterans) have no different risks of fathering several affected babies than nonveterans (4.3% versus 5.5% affected siblings, $p > 0.05$; Table 54); likewise, Vietnam veterans have no different risks than other men (3.9% versus 5.1% affected siblings, $p > 0.05$). Those men who reported that they had been exposed to Agent Orange had a significantly higher risk of fathering more than one affected baby than other men (11.3% versus 4.7%, $p < 0.05$).

The defects reported among the siblings of the seven index babies whose fathers said that they had been exposed to Agent Orange do not form any particularly coherent pattern. The defects in the index babies (according to the MACDP) and in the later born siblings (according to the mother) for these seven families are: 1) clubfoot in the index baby, heart murmur in the sibling, 2) omphalocele and tongue anomaly in the index baby, heart valve anomaly in the sibling, 3) tracheo-esophageal stenosis, heart murmur, 4) hydrocephalus, heart murmur, 5) ventricular septal defect, heart murmur, 6) anomaly of the biliary system, patent ductus arteriosus, and 7) complex cardiovascular anomalies, heart murmur.

Logistic regression analyses of the data regarding risks for fathering several affected babies associated with the Exposure Opportunity Indices (Table 55) yielded negative nor significant betas.

3.2.3 Secondary Adjusted Analyses

The Secondary Adjusted analysis consisted of searching the 108 covariables listed in Table 6 for possible confounding effects. As specified in section 2.8, this search was done on a defect-by-defect, hypothesis-by-hypothesis, variable-by-variable basis, using the Mantel-Haenszel procedure. First, a Mantel-Haenszel odds ratio estimate for a particular hypothesis and defect group (without consideration of any covariable) was computed; for this estimate, the data were stratified on hospital and period of birth and on race, just as in the Basic logistic regression analyses. Second, another Mantel-Haenszel odds ratio was computed, with the data stratified on hospital, period of birth, race, and the covariable. This latter odds ratio may be thought of as being "adjusted for" the covariable. The two odds ratios were then compared. In all, 61,992 of these comparisons were made (95 defect groups x 6 hypotheses x 108 covariables + the All Case Babies group x 4 hypotheses x 108 covariables). For this part of the data analysis, the Agent Orange Exposure Opportunity Indices were "collapsed" into two categories — one comprising scores of 0 and 1, and the other, scores of 2 through 5. The analytical plan called for further consideration of those covariables whose inclusion resulted in a 1.5-fold (or 0.67-fold) or greater change in the odds ratios. This was to take place

in logistic regression analyses, along with any other covariables which resulted in changes for particular hypotheses and defect groups.

In all, 451 of the 61,992 comparisons met the criterion, but the nature of the specific instances that yielded 1.5-fold (or 0.67-fold) odds ratio changes dictated that no logistic regression analyses be done. In general, the only comparisons that met the criterion of a 50% change in the odds ratio were those associated with hypotheses and defect groups in which there were very small numbers of "exposed" cases, usually 1 to 3. Including one or more variables in a logistic regression based on no more than a handful of "exposed" cases would be of no value to the inferential process at hand, and might even be considered inappropriate. Table 56 presents the distribution of all 61,992 comparisons by numbers of "exposed" fathers and the magnitude of the changes in the odds ratios that resulted from consideration of the 108 covariables. In 271 analyses, consideration of a particular covariable resulted in an odds ratio that was <0.667 as large as the unadjusted odds ratios; all but two of these instances occurred in analyses in which there were fewer than five "exposed" cases or controls. Similarly, in 179 instances, the odds ratios adjusted for particular covariables were ≥ 1.501 times larger than the unadjusted ratios, and all changes of this magnitude derived from tests that involved fewer than five "exposed" cases or controls (Table 56).

The two instances in which consideration of a covariable changed the odds ratio by a factor of 0.667 or more, tabulated in the "Five or More" column of Table 56, were: 1) maternal age for the Veteran Status hypothesis for Down's Disease, and 2) paternal age for the Veteran Status hypothesis for the Dominant Mutations defect group. Therefore, further analyses would be superfluous: maternal age adjustments were done as a part of the Primary Adjusted analyses for Down's Disease, and no Vietnam veterans were among the fathers of babies with syndromes thought to be due to fresh dominant mutations.

3.2.4 Search for Vietnam Veteran Birth Defect Syndrome

The search for a syndrome of defects unique or overrepresented among the case babies born to Vietnam veterans did not reveal such a syndrome. The search was motivated by the usual pattern of developmental disruption caused by typical teratogenic agents. Most known teratogens act by disrupting fetal development early in gestation, and usually cause a specific syndrome of defects. Rubella causes a unique clustering of defects. Thalidomide caused a specific pattern of malformations. As noted earlier, the relevance of this principle to paternally derived developmental problems is unknown; nevertheless, a search seemed warranted.

The search consisted of comparing the frequency of Vietnam veterans among the fathers of case group babies with specific pairs and triplets of defects with the frequency of Vietnam veterans among the fathers of control group babies. Pairs and triplets of defects were defined as two and three defects occurring in the same baby; the pairs and triplets were based on combinations of all of the ICD-8 defect codes listed in Table 1.

Among the 4,992 case group babies whose mothers completed interviews through the military history section, 3,069 unique pairs and 4,089 triplets of defects occurred. For many babies, only one defect was recorded, but under MACDP registry procedures up to 12 separate codes can be recorded. A baby with only one defect code does not contribute to this analysis, a baby with two defects contibutes one pair, and a baby with three defects contibutes three pairs and one triplet. A baby with 12 defects coded will contibute 66 pairs. About 80% of the defect pairs and 90% of the defect triplets occurred only in babies born to non-Vietnam veteran fathers. The statistical significance of the difference in the frequency of Vietnam veteran fathers among the fathers of babies with pairs and triplets of defects was assessed by chi-square test, with Yates' correction. Of those pairs yielding probability values of less than

0.05, all but three had only one or two affected babies born to Vietnam veteran fathers. One of the pairs, composed of defects coded 7515 ("Other Anomaly of Intestine") and 7540 ("Clubfoot"), affected no babies born to non-Vietnam veterans and three born to Vietnam veterans. A second pair, 7560 ("Other Anomalies of Skull and Face Bones") and 7561 ("Anomalies of Spine"), appeared in three babies born to Vietnam veterans and in five born to non-Vietnam veterans. The third pair was of codes 7452 ("Other Specified Anomalies of Ear") and 7561, which affected 5 babies of Vietnam veterans and 16 babies of non-Vietnam veterans. None of the triplets of defects which had probability values of <0.05 affected more than two babies born to Vietnam veterans. Overall, these findings are not surprising and merit no further analysis.

3.2.5 Malaria and Malaria Prophylaxis

Paternal reports of contracting malaria while in Vietnam were significantly related to case/control status for Total Sex Organ Defects, and Hypospadias, according to the results of the Mantel-Haenszel tests used for the initial analysis of this issue (the Total Sex Organ Defects group is largely composed of babies born with hypospadias). Both of the associations suggest that men who reported having malaria may have an increased risk for fathering babies with these defects. The tests for these two groups were repeated by using conditional logistic regression. The results of these regression analyses, which confirm the Mantel-Haenszel findings, are presented in Table 57. These findings are, of course, based on fathers' reports of malaria; they have not been confirmed in any way, as, for example, by review of military medical files. Each man who reported that he had contracted malaria was, however, asked what treatment he had received. By and large, the descriptions of treatment received add credence to the reports of the disease. A relatively large proportion of the men who reported having contracted malaria also reported that they believed that they had been exposed to Agent Orange—48%, in contrast to 21% of those who did not have malaria. A large proportion of mothers with babies with defects classed by the MACDP in the Total Sex Organ Defects and Hypospadias group said that their babies were not affected (Table 42). The proportion of mothers disagreeing with the MACDP records was the same for babies whose fathers did and did not report malaria.

The Mantel-Haenszel analyses for the association between reports of taking malaria prophylaxis and defects did not yield any significant associations.

4. DISCUSSION

The most important conclusion to be drawn from the analyses of this study's data is that they contain no evidence to support the position that Vietnam veterans have a greater risk than other men for fathering babies with all types of serious structural birth defects combined. Many fathers, whether Vietnam veterans or not, have had the misfortune of fathering babies with birth defects. In section 1.1 of this report, we estimated that perhaps 50,000 to 160,000 babies born to American Vietnam veterans over the past 10 to 15 years have had serious defects. This estimate is based only on the number of men who served in Vietnam, some simple assumptions about their fertility, and the usual "background" risk that a baby will be born with a defect. This study cannot prove that some factor associated with service in Vietnam was or was not associated with the occurrence of rare types of defects, of defects in the babies of selected individuals, or in the babies of small groups of veterans. The conclusion that Vietnam veterans, in general, have not fathered babies with all types of birth defects combined at higher rates than other men is, however, based on relatively strong evidence, and Vietnam veterans need to be made aware of this. In particular, those Vietnam veterans who have avoided starting a pregnancy because of fear of being particularly at risk of fathering a baby with a serious defect should know that their risk does not seem to be other than usual.

This study has not identified the causes of the birth defects that have occurred in the babies of Vietnam veterans, nor in the babies of men who did not serve in Vietnam. The causes of the vast majority of birth defects remain unknown. Two to three percent of the babies born to Vietnam veterans in the future will have serious birth defects, just as will a similar proportion of babies born to other men. The discovery of the causes of these defects—discovery that may make prevention possible—will depend on other research.

This study also provides little support for the notion that those men who may have been exposed to Agent Orange in Vietnam have had an increased risk of fathering babies with most specific types of defects. The conclusion regarding the possibility of Agent Orange-associated risks is based on considerably weaker evidence than the conclusion about Vietnam veterans in general, but the absence of any major increase in apparent risks in association with the (imperfect) measures of exposure used for this study also needs to be communicated to Vietnam veterans.

In evaluating these conclusions, the following factors need to be considered: the strengths and limitations of the study design, the possible effects of nonparticipation, the accuracy of the data collected, and the appropriateness of the analytical procedures. In addition, findings need to be considered in the context of other studies related to the issue at hand.

4.1 STRENGTHS AND LIMITATIONS OF THE STUDY DESIGN

The case control study, a standard design for epidemiological investigations, has certain strengths and weaknesses. The case group babies derived from CDC's registry of babies born with birth defects in the Metropolitan Atlanta area. This registry is a unique national resource without which this study would not have been possible. Even though this study is based only on families that had babies in the Atlanta area, there is no known reason why the results should not apply to Vietnam veterans residing elsewhere. However, use of the registry, which is primarily designed to collect data on babies born with structural birth defects, has precluded our drawing inferences on a variety of reproductive issues about which Vietnam veterans have expressed concern. Issues of infertility, spontaneous abortion, and physical or mental deficits which only become apparent later in childhood are not addressed by this study. None-

theless, the defects of babies that are ascertained by the registry include the majority of the infant and childhood problems in which interest has been shown, and in many respects these problems can be considered the most important of Vietnam veterans' concerns for their reproductive health.

Insofar as ascertainment by the registry is complete, the study is based on all babies born with serious defects in a population of some 323,000 births occurring in the Atlanta area from 1968 through 1980. This very large case control study had a very high statistical power to detect rather small increases in the risk for Vietnam veterans for fathering babies with all types of defects combined. Since roughly 10% of study fathers were Vietnam veterans, the study may be thought of as having a sensitivity similar to that of a cohort study that ascertained defects among 32,300 babies born to Vietnam veterans (and in a large number of babies born to men who did not serve in Vietnam), a study that would have been much more difficult to complete than the one done.

Another major advantage of the study design is that there is little concern about bias (associated with Vietnam veteran status) in the ascertainment of birth defects in the study babies. In any cohort study, this would be a major concern; duplicating the MACDP hospital chart review for such a large number of babies born to Vietnam veterans and suitable control fathers probably would not be feasible, and ascertainment, therefore, would have to depend on parents' reports of defects.

4.2 POSSIBLE EFFECTS OF NONPARTICIPATION

It is rare indeed that an interview-based study achieves a participation rate approaching 100%, and this study was no exception. The general participation rates achieved, however, essentially met the overall goals set when the study was started. The participation rate for White race parents was higher than that for Other race parents. The rate for White race mothers was 75% and for White race fathers, 66%, whereas for Other race mothers, the rate was 58% and for Other race fathers, 32%. The lower rate for Other race parents may reduce our ability to generalize about the study results, particularly for issues that depend on completed paternal interviews.

Any study in which data are not collected from all of those chosen as participants at the outset engenders concern that biases have been introduced. For this study, that concern is mitigated to a large degree by the fact that the participating case and control group parents were remarkably similar in many respects. In particular, the case and control group participation rates were very similar with respect to the sampling design variables of time of birth and hospital of birth. The only major difference found was that Other race control group parents participated more frequently than Other race case group parents, but this was shown to be of little concern with respect to possible influences on the analyses of the major study hypothesis. The major reason for nonparticipation was failure to locate the desired parents. The difficulty of locating them was to be expected, since the locating information that had to be used (e.g., parental addresses taken from birth records) was, on the average, several years old when the interviews were done. The fact that participation was essentially equal for case and control group families may have derived in part from efforts to keep (1) the tracing information used for case and control groups alike and (2) the tracing and interviewing staff "blind" as to the case/control status of families.

These statements are not to be construed to mean that the parents who could not be located (or who, once located, would not participate) are not different from those who did complete interviews. That they are different was shown for several factors (e.g., race, year of index birth), and they probably differ in many other ways. The major issue here is whether the

case group parents who did participate are somehow systematically different from the control group parents who participated, different in such a way that the relative risk estimates which derive from the comparisons of the two groups give a biased picture of the truth. There is no evidence in the study data to suggest that case/control differences are connected with differential participation that would give rise to any major biases.

Even so, an example of possible biases that could result from nonparticipation may be useful. Recall that higher participation rates were obtained for the families of those babies whose fathers' names were available from the study records and for families of White race babies. Interviewed mothers of babies whose records contained fathers' names, and mothers of White race babies, tended to be older and better educated. Recall also that the (interviewed) mothers of babies with veteran fathers tended to be older and better educated than the mothers of babies with nonveteran fathers. The families whose mothers' interviews were completed early in the data collection phase of the study were more likely to have veteran fathers than families whose mothers' interviews were completed late. These observations lead to the proposition that Vietnam veterans are less common among the fathers of families that did not participate.

But suppose that the frequency of Vietnam veterans among the fathers of nonparticipant case group families is the same as that observed for participant families, 10% Vietnam veterans. Further, suppose that the frequency for nonparticipant control group families is 50% less than that for participant control group families, or 5% Vietnam veterans. This hypothetical situation is one way in which the case and control group participants could be systematically different—the case group participants would accurately reflect the true frequency of Vietnam veteran fathers in the target population of all case group families but the control group participants would overestimate it. Such a situation would result in a true odds ratio (relative risk estimate) of about 1.2 in the participants and nonparticipants combined. The odds ratio observed for Vietnam veterans among the study participants for all defects combined was about 1.0 (Table 52). Thus, even under an assumption of what are considered rather extreme and unlikely differences in the frequency of Vietnam veterans for nonparticipant case and control group fathers, the relative risk would remain rather close to 1.0, and the extra risk would still be considerably lower than the usual or "background" risk.

4.3 DATA VALIDITY: POSSIBLE BIASES

There seems to be relatively little reason to be concerned about biases introduced by nonparticipation, but what of the validity and potential biases of the information provided by those who did complete interviews? The data on some of the "exposures" of interest had to be collected from parents, not from some external source. In most case/control studies, there is fear that members of the case and control groups will not give "exposure" histories with equal accuracy, thereby introducing bias into the case/control comparisons. For the major "exposure" in this study, paternal military service in Vietnam, there is little reason to have any substantial worry about the accuracy of either case or control group parents' reports. Indeed mothers appear to have been able to provide the same answers as fathers to the questions about fathers' military service, a fact that justified the use of the larger sample size of the "M" data base for the tests of hypotheses regarding risks for veterans and Vietnam veterans.

For the data collected with respect to self-reports of Agent Orange exposure, there must be concern for bias; there must also be concern for the validity of the reports; and for the possibility of Agent Orange exposure as measured by the Agent Orange Exposure Opportunity Index, there must be concern about validity, if not for bias.

The potential for bias in the analyses of the self-reports of Agent Orange exposure has presumably been reduced by avoiding the use of the parents of babies born without defects as controls. We do not know, however, just how successful this technique was. The technique might fail if parents with babies with various types of malformations had differing levels of recall, depending on the seriousness of the defects in their babies. It would also fail if Agent Orange exposure caused an increase in the risk for most or many different defect types. On the basis of our current limited understanding of how birth defects occur, this latter possibility seems unlikely. However, our present understanding is based almost solely on human experience or animal experiments in which environmental exposures cause problems through maternal/fetal exposure. It is possible that different pathogenetic mechanisms result from paternal exposures.

Vietnam veterans' ability to give valid reports of exposure to Agent Orange is a matter for debate. In addition, some will also hold that only a very small proportion of Vietnam veterans had a potential for exposure. Instead of entering these debates, we chose to listen to the reports of Vietnam veterans and make comparisons that should reduce possible case/control response biases. There is no way to assess the validity of the reports, but Vietnam veterans' answers to the question were generally consistent with their answers to other questions that would seem to indicate their potential for exposure. If a substantial increase in risk had been found, Vietnam veterans might have felt, with some justification, that it would be incumbent on others to prove that their reports were invalid. Between a quarter and a third of Vietnam veterans who participated in this study said that they had been exposed. This is a sizable fraction, and many of them probably feel that this exposure has placed them at some risk for some sort of reproductive health problem. It is a strength of this study that their assessment of exposure was used in the analysis.

The validity of the Agent Orange Exposure Opportunity Index is unknown. Does an index score of 5 invariably indicate a higher degree of exposure than a score of 4?, than a score of 1? Does it even invariably indicate greater opportunities for exposure? These questions cannot be answered today, and probably never will be answered. The records that must be used today to estimate exposure possibilities were made for military purposes, not for health studies. The index scoring, however, was done by service personnel familiar with existing records that document the use of herbicides in Vietnam by time and place. This staff also had personnel files from which to document Vietnam veterans' occupations and military units and records from which to estimate the locations of the units at various times. Moreover, a separate index scoring was assigned on the basis of location and occupation information taken from the men during the interviews. Again, information taken from veterans was used, and this is considered a strength of the study. Finally, the service staff assigned the scores without knowledge of the case/control group status of the individual veterans, and there can be no question about scoring biases connected with case/control status, as there is in respect to the self-reports of Agent Orange exposure. There was, however, a modest degree of agreement between the index scores and the self-reports of Agent Orange exposure. Again, this (albeit imperfect) measure of exposure opportunities was not found to be associated with any substantial increase in the risk for fathering babies with all types of defects combined.

In addition to considering the possible inaccuracies in the various "exposure" variables, we also need to consider the possibility that case and control group babies were misclassified. Misclassified case group babies are those who were registered by the MACDP but who did not have a birth defect; misclassified control group babies are those who were not registered by the MACDP but who did have a birth defect. The only measures of misclassification available for this study are the opinions of the interviewed mothers and fathers. The opinions of in-

terviewed mothers were reviewed, and they presented some difficult analytical decisions. For both case and control groups, some parents whose opinions were at variance with the study definitions are undoubtedly correct, and some are undoubtedly incorrect. Insofar as the parents' opinions are correct, the case group is "contaminated" with babies without defects and the control group is "contaminated" with babies having defects. This misclassification could reduce our ability to detect an association between the "exposure" variables and the occurrence of defects. After we examined the association of the opinions of the index babies' mothers with the veteran status of the fathers' and the mothers' age and education, we decided to proceed with the major part of the analysis, using the original study case-control definitions of cases and controls.

Mothers of case babies simply may not know that their baby did indeed have a defect, or they could deny the fact. On the other hand, the mothers could be correct, and the baby's registration by the MACDP the result of mistaken diagnoses written in hospital charts by physicians. We favor the position that, in most instances, the MACDP designator is correct. The situation regarding control babies is less clear. It would seem that a defect well described by a mother is a fair indication that a defect is present. This point of view is favored by the fact that most of the defects the mothers of control index babies described were those that are often diagnosed and cared for outside of hospitals (MACDP generally requires defect documentation in hospital charts). It is by no means clear, however, that the opinions of mothers of control group index babies are invariably correct. The ultimate solution to the problem would require extensive and impractical review of hospital charts, and contacts with attending physicians. We decided that it would be best to do the bulk of the analyses by using the study case/control designations. Supplementary analyses were done for those categories of defects in which there was a high degree of disagreement between the mothers' opinions and the study designations: Total Sex Organ Defects, Hypospadias, and Clubfoot. In addition the analysis for the "All Case Babies" group was redone. These supplementary analyses consisted of logistic regressions from which the suspect case and control group families were removed. In none of these reanalyses was there any marked change in the results.

Another attempt was made to reduce misclassification of case group babies. For several defect types, notably ventricular septal defect, patent ductus arteriosus, and clubfoot, diagnoses of "probable" and "possible" are not infrequent; these cases have been registered by the MACDP and they were included in the study. These cases have been removed for supplementary analyses, and these analyses did not give cause to revise the inferences drawn. An analysis of the "All Case Babies" group was also redone after these suspect case babies had been removed, and the estimated risks did not differ from those found when they were included.

4.4 ANALYTICAL APPROACH AND TOOLS

The Basic level of analyses was done by using conditional logistic regression (Breslow and Day, 1980). The reason for using conditional regression rather than unconditional logistic regression is that the latter is known to produce biased estimates of the odds ratio when the data are sparsely distributed (Breslow and Day, 1980) over the range of the covariables included in the analysis. This study had a sampling design in which controls were frequency matched to cases by hospital of birth, time of birth, and race. It is desirable to maintain this matching in the analysis, and therefore the data were rather sparse when considered on a stratum-specific basis. The advantage of unconditional over conditional logistic regression is that it does not require nearly as much computation time. Indeed, the approach used here

would have been infeasible without the efficient conditional logistic regression algorithm recently described by Gail et al. (1981).

The actual stratification used in the analyses was not exactly like that used to sample controls from among all births. Complete stratification was maintained on race and hospital of birth, but time of birth was collapsed into three 52-month periods. Time of birth was frequency matched in part because we believed that time of birth would be related to the likelihood that fathers would be Vietnam veterans, related to parents' memories of crucial preconceptional and gestational events, and furthermore, to trends in the incidence of certain defects (Oakley et al., 1983). In addition, we believed that the location of families would be related to time of birth. Since a good case/control balance was achieved on year-by-year participation rates, the need for maintaining year-by-year matching does not seem as important as grouping the data into a smaller number of categories to facilitate the assessment of the possibility that Vietnam veterans' risks varied over birth periods. In addition, the considerations of memory and so on seem to be well served by collapsing time of birth into three categories. On the other hand, no logical way to collapse the hospitals into groups could be identified, and the 20 hospital strata were maintained. Thus, the data were divided into 120 strata for all of the analyses at the Basic level (and at the Primary and Secondary levels as well). This had the effect of excluding substantial numbers of controls, but not many cases for all of the defect groupings except for "All Case Babies." For the "All Case Babies" analyses only 16 cases and 2 controls were lost because there were no matching cases or controls. For the other defect groupings, only a few cases were lost because there were no controls in specific strata, but all controls in a particular stratum were lost if there were no cases in that stratum. As pointed out before, this is really of no concern, since the control-to-case ratio was high even after the controls were excluded. This ratio was rarely less than three or four controls per case, and for the defect groups with the smaller numbers of cases the ratios became as high as 40 to 1 (see Table 52).

As noted, the frequency matching done at the time that control group babies were chosen applied to all case babies combined, but for individual defect categories there was no intentional frequency matching. At most, there is a "quasi matching" of case and control groups for specific types of defects. Thus, one might question the need to do the analyses while the stratification on the sampling design variables was maintained. As pointed out, there is little concern for the numbers of controls. In any case, it would almost certainly be desirable to maintain the stratification on race and period of birth. The question is, then, what is the need for maintaining the stratification on hospital of birth, and if there is no need, what effect does this stratification have on the analyses? The primary effect would be to reduce the statistical efficiency of the analyses, making it more difficult for a particular odds ratio to reach statistical significance. This effect would probably not be large, and we did not believe that it was reason enough to abandon the stratification on a variable that had at least been used as a "quasi matching" variable. For those who disagree with our maintaining stratification on the sampling design variables for specific defect groupings, data in Table 52 can be used to compute odds ratios and probability values for the simple 2 X 2 table for each hypothesis for each of the 96 defect groupings. In general, there is relatively little difference in the statistics that derive from the simple 2 X 2 tables and from the stratified analyses, but there are exceptions. For example, the odds ratio for the risk for veterans (excluding Vietnam veterans) for fathering babies with spina bifida computed from the (unstratified) numbers presented in Table 52 is 1.48, with a chi-square of 6.53 ($p<0.05$; to derive this odds ratio and chi-square, we took cases from the Spina Bifida section of Table 52, whereas we took controls from the All Case Babies section). The logistic regression odds ratio estimate for spina bifida computed from

the stratified data is 1.25, with confidence limits that overlap 1.0 ($p > 0.05$). We prefer the risk estimate derived from the stratified data on the a priori grounds that spina bifida incidence varies with racial background, and veteran status was shown earlier to be associated with race, but those who think otherwise can make their own computations from the data in Table 52.

The Primary Adjusted analysis was also done with conditional logistic regression, in a manner similar to that used for the Basic analysis, but with three more covariables: age of mother, education of mother, and alcohol consumption of the mother. In particular, the stratification on hospital of birth, period of birth, and race was maintained. The three new covariables were chosen by a group of birth defects specialists before the start of data analysis. In addition, the group also chose the variable birth defects in the first-degree relatives of index babies, but for a variety of reasons this variable could not be treated simultaneously with the other three "essential" variables in the logistic regression analyses.

The analytical tool for the Secondary Adjusted analysis was different. Logistic regression could not be used because of the massive amount of computer time that would have been required—the efficiency of the logistic regression algorithm, mentioned above, is only relative, and many hours of computer time were required to complete the Basic and Primary Adjusted analyses. The analytical plan called for the evaluation of the effects on the risk estimates of each of 108 covariables. This number, made possible by the wide-ranging questionnaires, is far too large to consider simultaneously in logistic regression analyses with the number of cases and controls available. The plan therefore called for separate consideration of each variable with a view to simultaneously evaluating a smaller subset in logistic regression analyses. The subset to be evaluated was to be composed of variables that caused 1.5-fold (or 0.67-fold) changes in the odds ratio for a particular hypothesis and defect group. Using logistic regression for this plan would have required computational resources equivalent to 108 times those used for the Basic or Primary analyses. Instead, we used a Mantel-Haenszel analysis, which requires fewer resources and less time. The approach was, for each hypothesis in each defect group, to first compute the odds ratio without considering a covariable (but with stratification on the sampling design variables). The results given by this approach were very similar to those obtained by the Basic level of the logistic regression, which it resembles. The next step was to compute the odds ratio with stratification on each of the 108 covariables. Any variable that resulted in a 1.5-fold (or 0.67-fold) change in the odds ratio was to be set aside, to be considered in a logistic regression analysis of that particular hypothesis for that particular defect group, along with other covariables that met the same criterion. As reported in section 3.2.3, however, no covariables met this criterion, save for hypotheses in defect groups with very small numbers of "exposed" cases. With such small numbers, we simply did not believe that anything could be gained from proceeding with the logistic regression step.

4.5 SIGNIFICANT TESTS OF HYPOTHESES AND STATISTICAL POWER

Even though the overall picture of the results of this study is that Vietnam veterans (and subsets of them described by their potential exposure to Agent Orange) are not at an increased risk for fathering babies with birth defects, we found some statistically significant results that may or may not be biologically significant. In considering these findings, it is necessary to keep in mind that there were many tests of hypotheses made for this study, and it was to be expected that there would be some statistically significant differences, even if there are no true differences in risk in the populations from which the study case and control group par-

ents are drawn. Statistical tests tell us how likely a given result is on the assumption of no true difference between the populations from which the groups being compared are drawn. Samples drawn from populations with no difference are expected to show a significant difference in a certain proportion of instances, a proportion equal to the level of "significance" (alpha level) chosen. In this study the alpha level used was 0.05. This means that we expect about 5% of independent tests to show significant differences even when there are no differences in the populations from which our samples are derived. Statistical testing is further discussed in Appendix B.

Many of the findings of this study seem to be consistent with the phenomenon just described. In specific instances, however, there is no way to tell whether a particular finding is one that arises from chance variation or from a true difference in the risks of the two groups being compared. One can only say, on the basis of the associated probability level, that a particular finding would only arise infrequently because of chance vagaries of the sampling process. Here, it seems appropriate to discuss the various statistically significant findings in the context of the several factors that need to be considered in the inferential process.

Alternatively, keep in mind that this study has only low power to detect modestly increased risks for defects affecting small numbers of babies. This is illustrated in Figures 9-10. These figures are similar to Figures 2 and 3, which were used in the study development phase to choose the number of controls. Figure 9 shows the statistical power for detecting various increases in risk for Vietnam veterans, and Figure 10, the power for detecting increases associated with self-reports of Agent Orange exposure. As the figures show, for all hypotheses tested for those categories of defects that have affected small numbers of babies, the power is low, except for rather high odds ratios.

These figures oversimplify the issue of power as it applies to this study. First, the assumption that case/control status or "exposure" status has not been misclassified is implicit. We believe that there is relatively little misclassification of case/control status, although some parents disagreed with the MACDP definitions. We also believe that there is relatively little misclassification of two of the "exposure" variables, veteran status and Vietnam veteran status. But in regard to the self-reports of Agent Orange exposure, misclassification may be considerable. Random misclassification will make it more difficult to detect any true association. On the other hand, nonrandom misclassification could result in the "detection" of false associations (misclassification is essentially a bias in the sense of the word used elsewhere in this report). Moreover, the computational procedures underlying the power figures required the assumption that the analysis is done with the data set out in a single 2 X 2 table instead of with the multiple strata used here; just how much this stratification affects power is unknown, but the amount is not thought to be too great. The power figures are not relevant to the Agent Orange Exposure Opportunity Index, since they pertain to 2 X 2 classifications of the data and the Exposure Opportunity analyses essentially entailed consideration of 2 X 6 tables. However, if there was an effect of Agent Orange exposure and there was a gradient in effect due to greater exposures, then this approach would be a more powerful one than a simple 2 X 2 classification. Even so, true exposures and perhaps even exposure opportunities are undoubtedly substantially misclassified by the index. The situation with respect to the power of the tests on the Exposure Opportunity Indices is not easily estimated.

4.6 COMMENTS ON SPECIFIC STATISTICALLY SIGNIFICANT FINDINGS

Vietnam veterans' risk for fathering babies with Complex Cardiovascular Defects according to the Basic level of analysis was lower (but not significantly lower) than the risk for other men. After adjustment for the three "essential" covariables in the Primary Adjusted analysis, the relative risk was found to be significantly less than 1.0 (Table 53). This was the only in-

stance in which consideration of the three "essential" covariables—maternal age, education, and alcohol consumption—resulted in the change of a nonsignificant association (i.e., at the "Basic" level of analysis) to a significant one.

Veterans (excluding Vietnam veterans) were found to be at lower risk for the defects included in the group "Total Sex Organ Defects" (Table 52). The point estimates of the relative risks for the specific types of defects which contribute to this group were all lower than 1.0, but none were individually significant, although for hypospadias the upper bound of the 95% confidence limit barely included 1.0. The results of the Primary Adjusted analysis were very similar. Many mothers whose babies belonged to this category said they felt that their baby did not have a defect. The repeat of the Basic analysis in which those cases were removed (and the controls where the mother said her index baby had a defect) showed essentially the same results.

An association of spina bifida risks with the two tests relative to the Agent Orange Exposure Opportunity Indices is noted. Here, risks seem to increase with increasing scores on the indices. As noted several times, the validity of the Exposure Opportunity Index is unknown. Moreover, although the betas for the indices for anencephalus are not significant, the point estimates are negative, indicating a lower risk for those men who had the higher index scores. Although the epidemiology and embryology of anencephalus and spina bifida differ in some respects, the defects are generally thought to be etiologically related (Carter, 1974). Thus, lack of an association between the indices and anencephalus gives cause to question the possibility that the association with spina bifida is other than a chance phenomenon.

Two tests of hypotheses regarding possible Agent Orange exposure for the defect coloboma indicated statistically significant increases in the risks for "exposed" fathers. Coloboma affected only a few babies, with an overall incidence rate of 0.08 per 1,000 live births in the Atlanta area during the study years. If one takes at face value the point estimate of around 4 for the relative risk of those who say that they were or may have been exposed to Agent Orange, the level of absolute risk would be roughly 0.3 per 1,000 births—only a small fraction of the background risk for all serious defects of 20 to 30 per 1,000 births.

The risks for Vietnam veterans for fathering babies with "Selected Ventricular Septal Defects" varied significantly over the birth periods, as did the risks associated with one of the Exposure Opportunity Indices and the self-reports of Agent Orange exposure test where the "yes" and "don't know" responses were pooled (Table 52; "Selected Ventricular Septal Defects" is a subset of all such defects formed by excluding "possible" and "probable" diagnoses). For the Vietnam veteran hypothesis and the self-reports of Agent Orange exposure hypothesis, the risks in the first birth period were significantly greater than 1.0, whereas the risks in the second period were nonsignificantly less than 1.0. If the true risks did indeed vary over the birth periods, then apparently the risks in the last period were normal (i.e., relative risks of about 1.0); from this, one might extrapolate that the risks in the future will also be normal.

The point estimates of the betas for both scorings on the Agent Orange Exposure Opportunity Index for patent ductus arteriosus (PDA) were both nonsignificantly negative, but there was period-specific variation in the risks. The risk for the Exposure Opportunity Index constructed from information obtained during interviews was significantly negative during the last birth period. This implies that Vietnam veterans with high index scores had a lower risk of having babies with PDA. Essentially the same results were obtained for "Selected" PDA, except that the 95% confidence limits for the third period beta barely overlapped 0.0 and was not, therefore, significant. PDA is in many respects an unusual defect. An open ductus arteriosus is a normal feature of fetal circulation, but it should close fairly soon after birth. Many

premature/low birth weight babies have problems because, in some way, their immaturity delays closure; in these instances, the PDA may not be considered a localized defect of development. In babies of normal weight, a ductus that does not close is considered a specific developmental abnormality. For this reason we excluded from this study babies with diagnoses of PDA who weighed less than 2,500 gm and who had no other defect.

Veterans (excluding Vietnam veterans) had a significantly higher risk than other men for fathering babies with cleft lip with or without cleft palate. Those men who had higher scores on the Agent Orange Exposure Opportunity Index based on interview-obtained information also had a higher risk for this defect, according to the results at the Basic level of analysis. The risk for veterans was present in the Primary Adjusted analysis, but the Exposure Opportunity Index association was reduced considerably and was not significant.

There was a significant difference in the race-specific risks for Vietnam veterans for "Selected Clubfoot"—White race fathers had a risk lower than 1.0 and Other race fathers had a risk above 1.0, but neither risk was individually significantly different from unity.

According to the Basic level analyses, Vietnam veterans had an increased risk for fathering babies with nail anomalies, but the point estimate of the risk was reduced considerably in the Primary Adjusted analysis and was not statistically significant.

Vietnam veterans who were scored on the Exposure Opportunity indices had a significantly higher risk for fathering babies with situs inversus. Only two such babies, however, were born to Vietnam veterans, and the use of a logistic regression on an index with five levels with such sparse data is questionable, at best. Moreover, the comments regarding the rarity of coloboma (see above) apply here as well.

Vietnam veterans' risk for having babies with congenital neoplasms was 1.8 (Table 52), with 95% confidence limits of 0.99 to 3.29. The risks associated with the higher levels of the Agent Orange Exposure Opportunity Index based on interviews were significantly higher than 1.0. The results of the Primary Adjusted analysis were very similar. None of the 108 covariables considered in the Secondary Adjusted analysis changed the odds ratios more than a few percentage points, indicating that these associations were not due to the confounding effects of the covariables available for review. The point estimates of the risks found here are rather low—of such a level that they could conceivably be the result of some unknown bias or confounding factor. They could be chance events, or they could be the result of some experience in the Vietnam service of fathers.

The unique analysis of the data for the possibility of a risk for Vietnam veterans in general, expressed by the birth of more than one affected baby, did not show any association. However, a significantly higher proportion of men who felt that they had been exposed to Agent Orange had a second affected baby (born after the affected index baby) than did other fathers of case group babies who felt they had not been exposed or who were not Vietnam veterans (Table 54). The accuracy of the mothers' reports of birth defects in the siblings of the index babies is unknown. As noted in the Results section, five of the seven subsequently born affected babies were said to have had heart murmurs, which may or may not represent substantial problems. Because the control group was expected to have and was found to have fewer families with affected babies born after the index baby than the case group, families in the control group were not used as a point of reference. Instead, the comparisons were done with case group families in which the fathers were not Vietnam veterans or said that they had not been exposed to Agent Orange. This approach is similar to that taken for the other analyses of the self-reports of Agent Orange exposure—an approach taken to reduce possible case/control bias. This association could be an expression of a case/"control" bias in which families with only one affected baby were less likely to report self-perceived exposure. The fact that

the Exposure Opportunity indices were not associated with the birth of more than one affected baby militates against a true association. Despite these reservations, however, this finding may represent a true effect of exposure.

As noted, there is an apparent association between malaria and hypospadias. Malaria infection was the single largest disease problem for military medicine in Vietnam (Neel, 1973). In December 1965, malaria hospitalization rates were at their peak of 98.4/1,000 troops per year. During subsequent war years, these rates generally decreased, with fluctuations due to seasonal conditions, operational areas, degree of contact with the enemy, and breakdowns in malaria prophylaxis discipline. According to Neel (1973), data summarized by year show that from 1966 through 1970 the annual rate of hospitalizations for malaria ranged from 15 to 45 admissions per 1,000 troops per year. In all, 52 Vietnam veteran fathers in this study reported that they had contracted malaria. The admission rates cited above are difficult to translate into an expected number for the 672 Vietnam veterans interviewed for this study, but the number observed does not appear to be unreasonable.

4.7 OTHER RELEVANT STUDIES

How do the results of this study compare with the results of related studies? The most directly comparable study is that of birth defects risks among Australian Vietnam veterans, conducted by the Commonwealth Institute of Health, University of Sydney (Donovan, 1983). It showed, in a matched pair design of 8,517 cases and controls, no increased risk of birth defects in babies fathered by men who served in Vietnam in the Australian Army. Results of two studies done in Vietnam also show no adverse reproductive effects. Kunstadter (1982) reviewed Vietnamese hospital records from 1962-1973 and found no increased frequencies of defects in babies born to mothers possibly exposed to herbicides. His study was not designed to determine the possible effects of exposure of fathers with respect to birth defects in their children. Tung (1971) reported histories of the families of North Vietnamese veterans who had served in sprayed areas of the south. He presented several case reports of children with birth defects whose parents stated that they were sprayed with herbicides. His description provided no opportunity for comparison with families exposed to herbicides who did not have children with birth defects. Other reports by this researcher have circulated in the U.S.A. in typescript form, but none have appeared in the published medical literature.

Other human studies, conducted outside of Vietnam, have considered male or female exposures to 2,4,5-T and other herbicides. Using data from the birth defect surveillance program in Hungary, Thomas (1980) examined associations with increasing use of 2,4,5-T in the Hungarian forestry industry. With 55% of the Hungarian population classified as rural and approximately 25% of the population engaged in agriculture and forestry, he was unable to demonstrate increases in the incidence rates of several selected defects. Birth outcomes, from 1969 through 1980, of families of professional male New Zealand 2,4,5-T sprayers were compared with those of other agricultural contractors (Smith et al., 1982), and birth defects risks were not found to be higher among the herbicide sprayers. The correlation between aerial spraying of 2,4,5-T by time and location was compared with the number of babies with malformations born in a population of 37,751 Northland, New Zealand, live births and stillbirths. No evidence for increased risk of birth defects was found, except in the case of clubfoot. That increase, however, occurred when exposure levels could not be readily determined, and the authors made no causal inference (Hanify et al., 1981). In the United States, an increase in the incidence of cleft palate in Arkansas and its possible relationship to the agricul-

tural use of 2,4,5-T was attributed to better case finding, not increased exposure to the herbicide (Nelson et al., 1979). In 1980, the wives of Dow Chemical workers were interviewed to determine reproductive outcomes. Townsend et al. (1982) compared the proportion of adverse reproductive outcomes in families of male workers with known exposure to dioxin with the proportion in families of Dow workers unexposed to dioxin. No association was found between exposure and adverse reproductive outcomes.

At present, no adverse human reproductive effects have been shown to be related to exposure to pheonoxy herbicides and dioxin. Evidence and concern for such ill effects come from animal experiments. These adverse outcomes occur by administering the chemicals to pregnant females at critical times during gestation (e.g., Courtney and Moore, 1971). In all animal experiments in which paternal exposures have been evaluated, results have been negative.

Two studies exposing male experimental animals to varying doses of 2,4,5-T and dioxin over varying intervals showed no difference in the frequency of congenital malformations in offspring sired by the exposed animals. Dioxin-exposed male and female rats studied in a three-generation experiment by Murray et al. (1979) showed no significant increase in congenital malformations. Lamb et al. (1980) fed male C57BL/6 mice several concentrations of a simulated version of Agent Orange for several weeks; these males were mated to unexposed females. No differences in the rates of congenital malformations in the offspring of the exposed and the comparison groups were observed.

From the few studies done, there is no conclusive evidence that 2,4,5-T or dioxin has caused adverse reproductive outcomes in humans. In certain animal species, when pregnant females were exposed, their offspring have had birth defects. However, in no species have fathers' exposures been shown to cause congenital defects in offspring.

The studies of human populations with well-documented exposure to herbicides and/or dioxin have included small numbers of people. Such small studies have only a weak ability to demonstrate even modestly increased risks. Therefore, the fact that none have been demonstrated may reflect the weaknesses of the studies rather than a true lack of effect. The present study included a relatively large number of people, but the estimates of Agent Orange exposure were probably rather inaccurate. Thus, the conclusions regarding possible Agent Orange-associated risks for Vietnam veterans that can be drawn from this study are rather weak.

This study does, however, provide strong evidence that Vietnam veterans, in general, are not at an increased risk of fathering babies with the aggregate of the types of defects considered. Thus, if any increased risks were caused by exposure to Agent Orange, they are small, limited to select groups of veterans, or occur only with specific rare types of defects.

5. TABLES

ABBREVIATIONS USED IN TABLES

Defect Descriptions

Abbreviations	*Full Description*
ABS HYPO UMBILICAL ARTERY	Absence or Hypoplasia of Umbilical Artery
ANOM ADRENAL GLAND	Anomalies of Adrenal Gland
ANOM EAR-IMPAIR HEARING	Anomalies of Ear Causing Impairment of Hearing
ANOM GALL-BLAD, BILE, LIVER	Anomalies of Gall-Bladder, Bile Ducts, and Liver
ANOM GREAT VEINS	Anomalies of Great Veins
ANOM INTEST FIXATION	Anomalies of Intestinal Fixation
ANOM JAW	Anomalies of Jaw
ANOM OTHER ENDOCRINE	Anomalies of Other Endocrine Glands
ANOM OVARY, FALLOP, UTERUS	Anomalies of Ovary, Fallopian Tube, and Uterus
ANOM PANCREAS	Anomalies of Pancreas
ANOM SKULL, FACE BONES	Anomalies of Skull and Face Bones
ANOM SPINE	Anomalies of Spine
ANOM THYROID GLAND	Anomalies of Thyroid Gland
ANOM UVULA	Anomalies of Uvula
ANOM VAGINA, EXT FEM GENIT	Anomalies of Vagina and External Female Genitalia
ATRES STEN RECT ANUS	Atresia and Stenosis of Rectum and Anal Canal
ATRES STEN SMALL INTEST	Atresia and Stenosis of Small Intestine
ATRES STEN URETHRA, BLAD	Atresia and Stenosis of Urethra and Bladder Neck
BRANCH CLEFT CYST FIST	Branchial Cleft, Cyst, or Fistula; Pre-auricular Sinus
DIS AMINO ACID PROT METAB	Disorder of Amino Acid and Protein Metabolism
DIS CARBOHYD METAB	Disorder of Carbohydrate Metabolism
DIS EXOCRINE GLANDS	Disorder of Exocrine Glands
DIS LIPID METABOLISM	Disorder of Lipid Metabolism
DIS METAB MINERALS	Disorder Involving Metabolism of Minerals
DIS RENAL TRANSPORT	Disorder of Renal Transport
DIS STEROID METAB	Disorder of Steroid Metabolism
EXSTROPHY URIN BLADDER	Extrophy of Urinary Bladder
GEN FLEXION CONTRACTURE	Generalized Flexion Contracture
MULT CONGEN ANOM UNSPEC	Multiple Congenital Anomalies, Unspecified
OBSTRUCT DEF URIN TRACT	Obstructive Defects of Urinary Tract
OST ATRIOVENTRIC COMMUNE	Ostium Atrioventriculare Commune
OTH ANOM INTEST	Other Anomalies of Intestine
OTH ANOM LARYN, TRACH, BRON	Other Anomalies of Larynx, Trachea, and Bronchus
OTH ANOM LOWER LIMB	Other Anomaly of Lower Limb
OTH ANOM LUNG	Other Anomalies of Lung
OTH ANOM NOSE	Other Anomalies of Nose
OTH ANOM OF NERVOUS SYS	Other Anomalies of Nervous System
OTH ANOM PERIPH VASC SYS	Other Anomalies of Peripheral Vascular System
OTH ANOM RIBS STERNUM	Other Anomalies of Ribs and Sternum
OTH ANOM UPPER LIMB	Other Anomaly of Upper Limb
OTH DEF ABDOMINAL CAVITY	Other Defect of Abdominal Cavity
OTH FORM MONSTER	Other Forms of Monster
OTH GEN ANOM SKELETON	Other Generalized Anomalies of Skeleton
OTH SPEC ANOM BLAD URETH	Other Specified Anomalies of Bladder and Urethra
OTH SPEC ANOM CIRC SYS	Other Specified Anomalies of Circulatory System
OTH SPEC ANOM DIGEST SYS	Other Specified Anomalies of Digestive System
OTH SPEC ANOM FACE, NECK	Other Specified Anomalies of Face and Neck
OTH SPEC ANOM GENITAL	Other Specified Anomalies of Genital Organs
OTH SPEC ANOM HEART	Other Specified Anomalies of Heart
OTH SPEC ANOM KIDNEY	Other Specified Anomalies of Kidney
OTH SPEC ANOM MUSC, TEND	Other Specified Anomalies of Muscle, Tendon, and Fascia
OTH SPEC ANOM OF EAR	Other Specified Anomalies of Ear
OTH SPEC ANOM OF EYE	Other Specified Anomalies of Eye

Abbreviations	*Full Description*
OTH SPEC ANOM RESP SYS	Other Specified Anomalies of Respiratory System
OTH SPEC ANOM SKIN	Other Specified Anomalies of Skin
OTH SPEC ANOM SPINAL CORD	Other Specified Anomalies of Spinal Cord
OTH SPEC ANOM UP ALIMENT	Other Specified Anomalies of Upper Alimentary Tract
OTH SPEC ANOM URETER	Other Specified Anomalies of Ureter
OTH SPEC ANOMALIES BRAIN	Other Specified Anomalies of Brain
OTH SPEC SYND	Other Specified Syndromes
OTH SPECIFIED CONG ANOM	Other Specified Congenital Anomaly
OTH SYND AUTOSOMAL ABNORM	Other Syndromes due to Autosomal Abnormality
OTH UNSPEC DIS METAB	Other or Unspecified Disorder of Metabolism
OTH UNSPEC HERNIAS	Other and Unspecified Hernias
OTH UNSPEC LIMB	Other and Unspecified Anomaly of Unspecified Limb
REDUCT DEF LOWER LIMB	Reduction Deformity of Lower Limb
REDUCT DEF UNSPEC LIMB	Reduction Deformity, Unspecified Limb
REDUCT DEF UPPER LIMB	Reduction Deformity of Upper Limb
SPEC ANOM HAIR	Specified Anomalies of Hair
SPEC ANOM NAILS	Specified Anomalies of Nails
SPINA BIFIDA W/OUT HYDRO	Spina Bifida without mention of Hydrocephalus
SPINA BIFIDA WITH HYDRO	Spina Bifida with Hydrocephalus
STEN ATRES PULMONARY ART	Stenosis or Atresia of Pulmonary Artery
SYND SEX CHROM ABNORM	Syndromes due to Sex Chromosome Abnormality
TRACHEO-ESOPH FIST ATRES	Tracheo-Oesophageal Fistula, Oesophageal Atresia and Stenosis
TRANSPOS GREAT VESSELS	Transposition of Great Vessels
UNSPEC ANOM CIRC SYS	Unspecified Anomalies of Circulatory System
UNSPEC ANOM DIGEST SYS	Unspecified Anomalies of Digestive System
UNSPEC ANOM FACE, NECK	Unspecified Anomalies of Face and Neck
UNSPEC ANOM GENITAL	Unspecified Anomalies of Genital Organs
UNSPEC ANOM HEART	Unspecified Anomalies of Heart
UNSPEC ANOM MUSCSKEL SYS	Unspecified Anomalies of Musculoskeletal System
UNSPEC ANOM OF CNS	Unspecified Anomalies of Brain, Spinal Cord, and Nervous System
UNSPEC ANOM OF EAR	Unspecified Anomalies of Ear
UNSPEC ANOM OF EYE	Unspecified Anomalies of Eye
UNSPEC ANOM SKIN, HAIR, NAIL	Unspecified Anomalies of Skin, Hair, and Nails
UNSPEC ANOM URIN SYS	Unspecified Anomalies of Urinary System
UNSPEC TORCH INFECT	Unspecified TORCH Infection
UNSPECIFIED ANOM UP ALIMENT	Unspecified Anomalies of Upper Alimentary Tract

Table 1. Numbers of Babies Born with Defects 1968-1980 and Registered by MACDP as of September 1981, by Category of Defect,[a] Type of Defect, Period of Birth, and Race

Type of Defect		Period of Birth[c]			Race[d]		
Code	Defect Description	01/68 - 04/72	05/72 - 08/76	09/76 - 12/80	W	O	Total
CATEGORY 1 DEFECTS:[b]							
7400	ANENCEPHALUS	109	69	61	201	38	239
7410	SPINA BIFIDA WITH HYDRO	82	47	52	158	23	181
7419	SPINA BIFIDA W/OUT HYDRO	64	43	21	101	27	128
7420	HYDROCEPHALUS	111	99	138	216	132	348
7430	ENCEPHALOCELE	19	18	28	46	19	65
7431	MICROCEPHALUS	32	50	61	67	76	143
7434	NEUROFIBROMATOSIS	0	4	3	4	3	7
7440	ANOPHTHALMOS	10	8	8	20	6	26
7441	MICROPHTHALMOS	17	30	36	45	38	83
7442	BUPHTHALMOS	7	4	3	4	10	14
7443	CONGENITAL CATARACT	7	17	45	38	31	69
7444	COLOBOMA	4	14	8	23	3	26
7445	ANIRIDIA	4	1	1	6	0	6
7450	ANOM EAR-IMPAIR HEARING	16	17	15	34	14	48
7460	COMMON TRUNCUS	7	11	12	24	6	30
7461	TRANSPOS GREAT VESSELS	39	41	49	97	32	29
7462	TETRALOGY OF FALLOT	32	21	42	67	28	95
7463	VENTRICULAR SEPTAL DEFECT	131	205	308	390	254	644
7464	ATRIAL SEPTAL DEFECT	58	92	139	181	108	289
7465	OST ATRIOVENTRIC COMMUNE	14	21	28	36	27	63
7466	ANOMALIES OF HEART VALVES	53	81	103	169	68	237
7467	FIBROELASTOSIS CORDIS	7	5	2	11	3	14
7470	PATENT DUCTUS ARTERIOSUS (PDA)[e]	94	156	368	248	146	618
7471	COARCTATION OF AORTA	39	37	36	85	27	112
7472	OTHER ANOMALIES OF AORTA	29	41	33	72	31	103
7473	STEN ATRES PULMONARY ART	26	34	68	73	55	128
7474	ANOM GREAT VEINS	18	20	23	45	16	61
7480	CHOANAL ATRESIA	8	12	14	23	11	34
7484	CONGENITAL CYSTIC LUNG	3	6	0	6	3	9
7485	AGENESIS OF LUNG	5	3	4	10	2	12
7490	CLEFT PALATE	64	70	69	143	60	203
7491	CLEFT LIP	47	36	34	94	23	117
7492	CLEFT PALATE + CLEFT LIP	80	86	70	190	46	236
7501	PYLORIC STENOSIS	129	197	128	412	42	454
7502	TRACHEO-ESOPH FIST ATRES	25	28	22	62	13	75
7511	ATRES STEN SMALL INTEST	33	30	41	64	40	104
7512	ATRES STEN RECT ANUS	51	47	44	103	39	142
7513	HIRSCHSPRUNG'S DISEASE	9	20	24	35	18	53
7514	ANOM INTEST FIXATION	20	23	31	49	25	74
7516	ANOM GALL-BLAD,BILE,LIVER	20	32	65	64	53	117
7517	ANOM PANCREAS	2	5	3	7	3	10
7520	INDETERMINATE SEX	0	3	3	4	2	6
7522	HYPOSPADIAS	238	301	313	662	190	852
7523	EPISPADIAS	6	11	11	17	11	28
7525	ANOM OVARY,FALLOP,UTERUS	10	11	11	26	6	32
7526	ANOM VAGINA,EXT FEM GENIT	19	22	33	36	38	74
7527	PSEUDOHERMAPHRODITISM	9	6	29	26	18	44

Table 1. Numbers of Babies Born with Defects 1968-1980 and Registered by MACDP as of September 1981, by Category of Defect,[a] Type of Defect, Period of Birth, and Race — Continued

Type of Defect		Period of Birth[c]			Race[d]		
Code	Defect Description	01/68 - 04/72	05/72 - 08/76	09/76 - 12/80	W	O	Total
CATEGORY 1 DEFECTS (Continued):[b]							
7530	RENAL AGENESIS	24	37	34	71	24	95
7531	CYSTIC KIDNEY DISEASE	28	28	25	52	29	81
7532	OBSTRUCT DEF URIN TRACT	37	57	53	93	54	147
7535	EXSTROPHY URIN BLADDER	5	6	5	12	4	16
7536	ATRES STEN URETHRA,BLAD	27	19	34	63	17	80
7540	CLUBFOOT	405	467	447	1,017	302	1,319
7552	REDUCT DEF UPPER LIMB	69	61	53	126	57	183
7553	REDUCT DEF LOWER LIMB	38	20	12	46	24	70
7554	REDUCT DEF UNSPEC LIMB	0	1	0	1	0	1
7558	GEN FLEXION CONTRACTURE	11	11	24	26	20	46
7564	CHONDRODYSTROPHY	9	8	9	16	10	26
7565	OSTEOGENESIS IMPERFECTA	8	4	2	10	4	14
7570	HEREDITARY OEDEMA OF LEGS	1	0	3	3	1	4
7573	SPEC ANOM HAIR	4	4	11	8	11	19
7574	SPEC ANOM NAILS	4	13	23	18	22	40
7580	ANOMALIES OF SPLEEN	13	22	33	36	32	68
7581	ANOM ADRENAL GLAND	3	5	3	9	2	11
7582	ANOM THYROID GLAND	11	8	14	27	6	33
7583	ANOM OTHER ENDOCRINE	4	7	10	10	11	21
7590	SITUS INVERSUS	8	8	7	8	15	23
7591	CONJOINED TWINS	6	4	1	9	2	11
7592	OTH FORM MONSTER	4	1	2	6	1	7
7593	DOWN'S DISEASE	111	112	95	212	106	318
7594	OTH SYND AUTOSOMAL ABNORM	20	17	32	39	30	69
7596	TUBEROUS SCLEROSIS	0	0	2	1	1	2
7598	OTH SPEC SYND	16	54	89	69	90	159
7599	MULT CONGEN ANOM UNSPEC	0	3	4	4	3	7
S603	DIAPHRAGMATIC HERNIA	35	38	34	65	42	107
S606	OMPHALOCELE	51	53	61	118	47	165
S621	OTHER NEOPLASM	18	42	66	96	30	126
S702	CYTOMEGALOVIRUS	7	7	5	12	7	19
S704	HERPES SIMPLEX	2	5	5	4	8	12
S705	SYPHILIS	17	6	11	3	31	34
CATEGORY 2 DEFECTS:[b]							
7432	OTH SPEC ANOMALIES BRAIN	20	19	36	50	25	75
7433	OTH SPEC ANOM SPINAL CORD	6	6	6	16	2	18
7438	OTH ANOM OF NERVOUS SYS	3	3	1	6	1	7
7448	OTH SPEC ANOM OF EYE	27	59	106	119	73	192
7452	OTH SPEC ANOM OF EAR	73	140	251	284	180	464
7458	OTH SPEC ANOM FACE,NECK	8	22	42	45	27	72
7468	OTH SPEC ANOM HEART	69	100	181	229	121	350
7469	UNSPEC ANOM HEART	38	57	53	100	48	148
7476	OTH ANOM PERIPH VASC SYS	8	23	26	37	20	57
7478	OTH SPEC ANOM CIRC SYS	1	5	2	7	1	8
7481	OTH ANOM NOSE	14	16	52	63	19	82

Table 1. Numbers of Babies Born with Defects 1968-1980 and Registered by MACDP as of September 1981, by Category of Defect,[a] Type of Defect, Period of Birth, and Race — Continued

Type of Defect		Period of Birth[c]			Race[d]		
Code	Defect Description	01/68 - 04/72	05/72 - 08/76	09/76 - 12/80	W	O	Total
CATEGORY 2 DEFECTS (Continued):[b]							
7483	OTH ANOM LARYN,TRACH,BRON	11	16	17	30	14	44
7486	OTH ANOM LUNG	21	26	56	51	52	103
7488	OTH SPEC ANOM RESP SYS	0	3	2	3	2	5
7493	ANOM JAW	59	76	115	175	75	250
7500	ANOMALIES OF TONGUE	14	20	25	39	20	59
7508	OTH SPEC ANOM UP ALIMENT	11	35	49	68	27	95
7515	OTH ANOM INTEST	10	24	37	48	23	71
7528	OTH SPEC ANOM GENITAL	33	57	103	136	57	193
7533	OTH SPEC ANOM KIDNEY	15	17	25	40	17	57
7534	OTH SPEC ANOM URETER	8	16	20	38	6	44
7538	OTH SPEC ANOM BLAD URETH	12	21	30	50	13	63
7551	SYNDACTYLY	107	89	98	219	75	294
7555	OTH ANOM UPPER LIMB	55	80	142	168	109	277
7556	DISLOCATION OF HIP	86	128	144	304	54	358
7557	OTH ANOM LOWER LIMB	73	103	216	225	167	392
7559	OTH UNSPEC LIMB	3	2	3	3	5	8
7560	ANOM SKULL,FACE BONES	48	81	111	184	56	240
7561	ANOM SPINE	29	51	67	93	54	147
7563	OTH ANOM RIBS STERNUM	19	41	42	70	32	102
7566	OTH GEN ANOM SKELETON	1	1	6	5	3	8
7568	OTH SPEC ANOM MUSC,TEND	25	27	32	54	30	84
7572	OTH SPEC ANOM SKIN	102	255	381	392	346	738
7595	SYND SEX CHROM ABNORM	4	10	13	22	5	27
S605	OTH DEF ABDOMINAL CAVITY	1	2	3	3	3	6
CATEGORY 3 DEFECTS:[b]							
7439	UNSPEC ANOM OF CNS	1	5	0	6	0	6
7449	UNSPEC ANOM OF EYE	1	2	4	6	1	7
7451	ACCESSORY AURICLE	128	226	285	407	232	639
7453	UNSPEC ANOM OF EAR	9	11	19	22	17	39
7454	BRANCH CLEFT CYST FIST	12	68	122	63	139	202
7455	WEBBING OF NECK	5	15	21	26	15	41
7459	UNSPEC ANOM FACE,NECK	1	5	6	10	2	12
7475	ABS HYPO UMBILICAL ARTERY	17	35	18	45	25	70
7479	UNSPEC ANOM CIRC SYS	0	1	1	2	0	2
7482	WEB OF LARYNX	0	1	2	1	2	3
7494	ANOM UVULA	6	1	5	8	4	12
7495	HIGH ARCHED PALATE	0	0	2	1	1	2
7509	UNSPEC ANOM UP ALIMENT	1	0	0	1	0	1
7510	MECKEL'S DIVERTICULUM	10	5	11	21	5	26
7518	OTH SPEC ANOM DIGEST SYS	3	0	1	4	0	4
7519	UNSPEC ANOM DIGEST SYS	1	1	0	2	0	2
7521	UNDESCENDED TESTICLE	55	85	157	193	104	297
7524	CONGENITAL HYDROCELE	18	51	115	126	58	184
7529	UNSPEC ANOM GENITAL	3	2	3	6	2	8
7539	UNSPEC ANOM URIN SYS	0	3	0	2	1	3
7550	POLYDACTYLY	476	508	701	279	1,406	1,685

Table 1. Numbers of Babies Born with Defects 1968-1980 and Registered by MACDP as of September 1981, by Category of Defect,[a] Type of Defect, Period of Birth, and Race — Continued

Type of Defect		Period of Birth[c]			Race[d]		
Code	Defect Description	01/68 - 04/72	05/72 - 08/76	09/76 - 12/80	W	O	Total
CATEGORY 3 DEFECTS (Continued):[b]							
7562	CERVICAL RIB	1	0	2	2	1	3
7569	UNSPEC ANOM MUSCSKEL SYS	0	0	1	1	0	1
7571	PIGMENTED NAEVUS	15	55	23	61	32	93
7579	UNSPEC ANOM SKIN,HAIR,NAIL	0	2	0	1	1	2
7588	OTH SPECIFIED CONG ANOM	0	2	0	0	2	2
S600	INGUINAL HERNIA	39	75	138	174	78	252
S602	UMBILICAL HERNIA	15	31	91	43	94	137
S604	OTH UNSPEC HERNIAS	4	9	20	19	14	33
S610	DIS AMINO ACID PROT METAB	11	12	18	18	23	41
S611	DIS CARBOHYD METAB	4	4	5	5	8	13
S612	DIS LIPID METABOLISM	1	0	0	1	0	1
S613	DIS STEROID METAB	6	1	6	7	6	13
S615	DIS METAB MINERALS	0	1	1	2	0	2
S617	DIS RENAL TRANSPORT	0	1	1	2	0	2
S618	DIS EXOCRINE GLANDS	11	20	12	39	4	43
S619	OTH UNSPEC DIS METAB	2	5	8	10	5	15
S620	HEMANGIOMA LYMPHANGIOMA	131	154	230	429	86	515
S700	UNSPEC TORCH INFECT	0	6	6	7	5	12
S701	RUBELLA	7	3	2	8	4	12
S703	TOXOPLASMOSIS	1	4	2	3	4	7

[a]See text for definition of defect categories.

[b]Babies with defects coded S701 or S703 and additional defects are only tabulated under S701 or S703.

[c]Three 52-month periods.

[d]W = White, O = Other.

[e]Tabulation includes all babies with PDA and other Category 1 defects. Babies with PDA and no other Category 1 defects were excluded if they weighed less than 2,500 gm; total registered babies with PDA was 1,160.

Table 2. Numbers of Eligible Study Families, by Case/Control Status and Race[a]

Race	Case/Control Status		
	Case	Control	Total
White	5,136 (72.0)	3,046 (71.7)	8,182 (71.9)
Other	1,997 (28.0)	1,200 (28.3)	3,197 (28.1)
Total	7,133 (100.0)	4,246 (100.0)	11,379 (100.0)

[a]Figures in parentheses are percentages of column totals.

Table 3. Computer Assisted Telephone Interviewing (CATI): Advantages and Disadvantages

Advantages:

- real-time logic, consistency, and range checks
- better data quality and fewer call-backs required
- real-time modification of questionnaire
- automatic skip-pattern implementation
- integration with tracing information
- improved interviewer monitoring
- quick access to data
- reduced paper to manage
- marginally reduced operating costs

Disadvantages:

- development time and cost
- reasonable typing speed required of interviewers
- computer intimidates some interviewers
- computer failures may require breakoff of interviews in progress
- questionnaires difficult to view in entirety

Table 4. Major Interview Items[a]

MOTHER'S INTERVIEW

Part 1 — First Interviewer

- pregnancy history
  - outcome (live born, miscarriage, etc.)
  - gestational period
  - birth weight
  - birth defects
  - cancer

Part 2 — Second Interviewer

- about the mother
  - occupational history
  - chronic diseases, medications
  - health during index pregnancy, medications
  - birth control before index pregnancy
  - alcohol, tobacco, illicit drug use
  - history of birth defects in family
- about the father
  - history of birth defects in family
  - occupational history
  - military service, Vietnam-related items
  - chronic diseases, medications
  - alcohol, tobacco, illicit drug use
- sociodemographic information

FATHER'S INTERVIEW

Part 1 — Third Interviewer

- pregnancy history
  - outcome (live born, miscarriage, etc.)
  - birth defects
  - cancer

Part 2 — Fourth Interviewer

- about the father
  - chronic diseases, medications
  - health before index pregnancy, medications
  - alcohol, tobacco, illicit drug use
  - occupational history
  - military service, Vietnam-related items
  - history of birth defects in family
- about the mother
  - occupational history
  - history of birth defects in family
  - chronic diseases, medications
  - health during index pregnancy
  - alcohol, tobacco, illicit drug use
- sociodemographic information

[a]See Appendix A for complete questionnaires.

Table 5. Examples of Agent Orange Exposure Opportunity Index Scores[a]

Index Score = 1 (minimum opportunities for exposures)

1. Service in selected locations at specific times
   (any job description except handling Agent Orange)
   e.g., Cam Ranh Bay (66)
   Qui Nhon (68-69)
   Nha Trang (67-68)
2. Non-Ranch Hand pilots and aircrew (66-67)
3. Specified Controlled Environments
   e.g., battalion surgeon (68)

Index Score = 2

1. Service in selected locations at specific times
   e.g., Gia Le (69-70)
   Phan Rang (other than 9-12/68,3-9/70)
   Qui Nhon (68-69)
2. Selected noninfantry occupations at specified places and times
   e.g., company clerk — Duc Pho (68-69)
   radio repairman — Chu Lai (66-67)
   truck driver — Cu Lam Nam (68)
3. Noninfantry stationed at selected bases with perimeter spraying
   e.g., wireman — Chu Lai (68-69)

Index Score = 3

1. Service at bases with perimeter spray operations, specified times
   e.g., Chu Lai (68-69) — Camp Eagle (68-69)
   LZ English (67-68)
2. Selected noninfantry occupations at specified locations and times
   e.g., salvage specialist — Danang (69-70)
   M.P. — Danang (68-69)
   wheeled vehicle mechanic — Long Binh (66-67)

Index Score = 4

1. Infantry/combat arms at specified locations and times
   e.g., An Khe (66-67)
   Tam Ky (67-68)
   Tay Minh (69-70)
2. Selected noninfantry at specified locations and times
   e.g., Helicopter pilot — Cu Chi (66-67)
   M.P. — Long Binh (67-68)
3. Advisors of Army, Republic of Vietnam Divisions (68-69)
4. Special Forces Camps (field personnel)
   e.g., Nha Trang (69-70)

Index Score = 5 (most numerous opportunities for exposure)

1. Infantry/combat arms at specified locations and times
   e.g., A Shau Valley (69)
   Tay Ninh (68)
   Phuoc Vinh (67)
2. Service at specified locations and times with aborted Ranch Hand missions or other herbicide mishaps
   e.g., Bien Hoa AFB (7/67,11/68)
   Long Binh Post (67-69)
   Phu Cat AFB (69-70)

[a]See text for description.

Table 6. List of Covariables for Secondary Adjusted Analysis, with Reference to Questionnaire Question Numbers[a]

Covariable	Question Number
Parity (4 levels)	M/Part 1
Unproductive Pregnancies (4 levels)	M/Part 1
Maternal Age (5 levels)	M/B-1a
Paternal Age (5 levels)	F/A-1
Hypothyroidism, Mother	M/B-5
Hyperthyroidism, Mother	M/B-5
Diabetes, Mother	M/B-5
High Blood Pressure, Mother	M/B-5
Rheumatic Heart Disease, Mother	M/B-5
Other Chronic Heart Disease, Mother	M/B-20
Epilepsy, Mother	M/B-5
Asthma, Mother	M/B-5
Cancer, Mother	M/B-11
Hypothyroidism, Father	F/A-5
Hyperthyroidism, Father	F/A-5
Diabetes, Father	F/A-5
High Blood Pressure, Father	F/A-5
Rheumatic Heart Disease, Father	F/A-5
Other Chronic Heart Disease, Father	F/A-18
Epilepsy, Father	F/A-5
Asthma, Father	F/A-5
Cancer, Father	F/A-10
Any Fever, Mother (-1/+3)	M/D-18,D-23,D-28,D-32
Kidney Infection, Mother (-1/+3)	M/D-21
Flu, Mother (-1/+3)	M/D-16
Any Fever, Father (-6)	F/C-4
Morning Sickness (+3)	M/C-1,C-2
Morning Sickness Medicines (+3)	M/C-5,C-6
Bendectin, Mother (+3)	M/C-6
Fertility Advice, Mother	M/C-11
Clomid, Mother	M/C-13
Fertility Advice, Father	F/B-9
Fertility Drug, Father	F/B-11
Any Contraception, Mother (-1/+3)	M/D-3,D-5,D-6b,D-9b,D-11b,D-12
Oral Contraceptives (-1/+3)	M/D-3
IUD (-1/+3)	M/D-5
Diaphragm (-1/+3)	M/D-6b
Any Spermicides, Mother (-1/+3)	M/D-6b,D-9b,D-11b
Cream/Jelly (-1/+3)	M/D-6b,D-9b
Contraceptive Foam (-1/+3)	M/D-11b
Contraceptive Insert (-1/+3)	M/D-12b
Pregnancy Test (Pill or Shot)	M/C-26
Prenatal Vitamins, Mother (-1/+3)	M/D-14,D-15
Blood Thinners, Mother (-1/+3)	M/D-38
General Anesthesia, Mother (-1/+3)	M/D-41
Any Tranquilizers, Mother (-1/+3)	M/D-42
Benzodiazepines, Mother (-1/+3)	M/D-42
Smoking, Mother (-1/+3)	M/D-50
Coffee-Tea, Mother (-3/+3)	M/D-59,D-61,D-62

Table 6. List of Covariables for Secondary Adjusted Analysis, with Reference to Questionnaire Question Numbers[a] — Continued

Covariable	Question Number
Alcohol Use, Mother (-1/+3)	M/D-55
Alcohol Consumption, Mother (3 levels) (-1/+3)	M/D-56,D-57
Binge Drinking, Mother (-1/+3)	M/D-58
Marijuana, Hashish Use, Mother (-1/+3)	M/H-34
LSD Use, Mother (-1/+3)	M/H-34
Cocaine Use, Mother (-1/+3)	M/H-34
Heroin, Methadone Use, Mother (-1/+3)	M/H-34
Death of Someone Close, Mother (-3/+3)	M/E-1
Divorce of Someone Close, Mother (-3/+3)	M/E-3
Job Loss of Someone Close, Mother (-3/+3)	M/E-5
2-3 Life Traumas, Mother (-3/+3)	M/E-1,E-3,E-5
3 Life Traumas, Mother (-3/+3)	M/E-1,E-3,E-5
Smoking, Father (-6)	F/C-15
Coffee-Tea, Father (-6)	F/C-24,C-26,C-27
Alcohol Use, Father (-6)	F/C-20
Alcohol Consumption, Father (3 levels) (-6)	F/C-21,C-22
Binge Drinking, Father (-6)	F/C-23
Marijuana, Hashish Use, Father (-3/+1)	F/G-36
LSD Use, Father (-3/+1)	F/G-36
Cocaine Use, Father (-3/+1)	F/G-36
Heroin, Methadone Use, Father (-3/+1)	F/G-36
Death of Someone Close, Father (-6)	F/D-1
Divorce of Someone Close, Father (-6)	F/D-3
Job Loss of Someone Close, Father (-6)	F/D-5
2-3 Life Traumas, Father (-6)	F/D-1,D-3,D-5
3 Life Traumas, Father (-6)	F/D-1,D-3,D-5
Maternal Education (3 levels)	M/I-5
Paternal Education (3 levels)	F/H-5
Agriculture/Forestry Industry, Mother (-1/+3)	M/A-5
Dyeing Industry, Mother (-1/+3)	M/A-5
Printing Industry, Mother (-1/+3)	M/A-5
Chemical Industry, Mother (-1/+3)	M/A-5
Agriculture Chemical Industry, Mother (-1/+3)	M/A-5
Rubber Industry, Mother (-1/+3)	M/A-5
Beauty Industry, Mother (-1/+3)	M/A-5
Health Industry, Mother (-1/+3)	M/A-5
Health Occupation, Mother (-1/+3)	M/A-3
Physician Occupation, Mother (-1/+3)	M/A-3
Nurse Occupation, Mother (-1/+3)	M/A-3
Teacher Occupation, Mother (-1/+3)	M/A-3
Hairdresser Occupation, Mother (-1/+3)	M/A-3
Air Attendant Occupation, Mother (-1/+3)	M/A-3
Any Occupation, Mother (-1/+3)	M/A-3,A-2
Agriculture/Forestry Industry, Father (-6)	F/E-4
Dyeing Industry, Father (-6)	F/E-4
Printing Industry, Father (-6)	F/E-4
Chemical Industry, Father (-6)	F/E-4
Agriculture Chemical Industry, Father (-6)	F/E-4
Rubber Industry, Father (-6)	F/E-4

Table 6. List of Covariables for Secondary Adjusted Analysis, with Reference to Questionnaire Question Numbers[a] — Continued

Covariable	Question Number
Beauty Industry, Father (-6)	F/E-4
Health Industry, Father (-6)	F/E-4
Physician Occupation, Father (-6)	F/E-2
Teacher Occupation, Father (-6)	F/E-2
Hair Dresser Occupation, Father (-6)	F/E-2
Forest, Farm, Garden Occupation, Father (-6)	F/E-2
Health Occupation, Father (-6)	F/E-2
Painter Occupation, Father (-6)	F/E-2
Printer Occupation, Father (-6)	F/E-2
Any Occupation, Father (-6)	F/E-2,E-1

[a]Questionnaires are found in Appendix A; "M" refers to mother's and "F" to father's questionnaire. For example, M/B-5 refers to question 5 of section B of the second part of mother's questionnaires. Except where noted, variables are dichotomous and generally reflect answers of "yes" and "no." Parents were considered to have chronic diseases (e.g., heart disease) if a diagnosis was made any time before the birth of the index baby. For acute problems and for drug and other similar exposures, a critical period in months around the time of conception of the index baby is specified. For example, a designation of (-6) indicates the 6-month period before conception, and (-1/+3) indicates 1 month before conception through the third month of pregnancy.

Table 7. Defect Groupings for Hypothesis Testing[a]

Category Title	Specific Defects Included[b]
ALL CASE BABIES	All case babies.
MULTIPLE DEFECTS[c]	Two or more defects in different ICD-8 code groups.
TOTAL NERVOUS SYSTEM DEFECTS	7400,7410,7419,7420,7430,7431,7434
TOTAL EYE DEFECTS	7440 - 7445
TOTAL CARDIOVASCULAR DEFECTS	7460 - 7467,7470 - 7474
COMPLEX CARDIOVASCULAR DEFECTS[d]	Two or more defects in range 7460 - 7479.
TOTAL RESPIRATORY DEFECTS	7480,7484,7485
TOTAL GASTROINTESTINAL DEFECTS	7490 - 7492,7501,7502,7511 - 7514,7517
TOTAL SEX ORGAN DEFECTS	7520,7522,7523,7525 - 7527
TOTAL URINARY TRACT DEFECTS	7530 - 7532,7535,7536
TOTAL MUSCULOSKELETAL DEFECTS	7540,7552 - 7554,7558,7564,7565,7570
TOTAL ENDOCRINE DEFECTS	7581 - 7583
AUTOSOMAL CHROMOSOME DEFECTS	7593 - 7594
DOMINANT MUTATIONS	Crouzon's disease; mandibulofacial dysostosis; aniridia; Milroy's hereditary lymphedema; acrocephalosyndactyly,types I,II; achondroplastic dwarfism; metatropic dwarfism; tuberous sclerosis.
ANENCEPHALUS AND SPINA BIFIDA	7400 - 7419
ANENCEPHALUS	7400
SPINA BIFIDA	7410 - 7419
HYDROCEPHALUS	7420
ENCEPHALOCELE	7430
MICROCEPHALUS	7431
NEUROFIBROMATOSIS	7434
ANOPHTHALMOS	7440
MICROPHTHALMOS	7441
BUPHTHALMOS	7442
CONGENITAL CATARACT	7443
COLOBOMA	7444
ANIRIDIA	7445
ANOM EAR WITH IMPAIRED HEARING	7450
CONUS ARTERIOSUS DEFECTS	persistent truncus arteriosus; aortopulmonary window; transposition great vessels; tetralogy of Fallot; pentology of Fallot; Eisenmenger syndrome.
COMMON TRUNCUS	7460
TRANSPOSITION GREAT VESSELS	7461
TETRALOGY OF FALLOT	7462
VENTRICULAR SEPTAL DEFECT (VSD)	7463
SELECTED VSD[e]	7463
ATRIAL SEPTAL DEFECT	7464
OSTIUM ATRIOVENTRIC COMMUNE	7465
ANOMALIES OF HEART VALVES	7466
FIBROELASTOSIS CORDIS	7467
PATENT DUCTUS ARTERIOSUS (PDA)	7470
SELECTED PDA[e]	7470
COARCTATION OF AORTA	7471

Table 7. Defect Groupings for Hypothesis Testing[a] — Continued

Category Title	Specific Defects Included[b]
OTHER ANOMALIES OF AORTA	7472
STEN ATRES PULMONARY ART	7473
ANOM GREAT VEINS	7474
CHOANAL ATRESIA	7480
CONGENITAL CYSTIC LUNG	7484
AGENESIS OF LUNG	7485
CLEFT PALATE	7490
CLEFT LIP W/WOUT CLEFT PALATE	7491 - 7492
PYLORIC STENOSIS	7501
TRACHEO-ESOPH FIST ATRES	7502
ATRES STEN SMALL INTEST	7511
ATRES STEN RECT ANUS	7512
HIRSCHSPRUNG'S DISEASE	7513
ANOM INTEST FIXATION	7514
ANOM GALL-BLAD,BILE,LIVER	7516
ANOM PANCREAS	7517
INDETERMINATE SEX	7520
HYPOSPADIAS	7522
EPISPADIAS	7523
ANOM OVARY,FALLOP,UTERUS	7525
ANOM VAGINA,EXT FEM GENIT	7526
PSEUDOHERMAPHRODITISM	7527
RENAL AGENESIS	7530
CYSTIC KIDNEY DISEASE	7531
OBSTRUCT DEF URIN TRACT	7532
EXSTROPHY URIN BLADDER	7535
ATRES STEN URETHRA,BLAD	7536
CLUBFOOT	7540
SELECTED CLUBFOOT[c]	7540
REDUCTION DEFORMITY	7552 - 7554
GEN FLEXION CONTRACTURE	7558
CHONDRODYSTROPHY	7564
OSTEOGENESIS IMPERFECTA	7565
HEREDITARY OEDEMA OF LEGS	7570
SPEC ANOM HAIR	7573
SPEC ANOM NAILS	7574
ANOMALIES OF SPLEEN	7580
ANOM ADRENAL GLAND	7581
ANOM THYROID GLAND	7582
ANOM OTHER ENDOCRINE	7583
SITUS INVERSUS	7590
CONJOINED TWINS	7591
OTH FORM MONSTER	7592
DOWN'S DISEASE	7593
OTH SYND AUTOSOMAL ABNORM	7594
TUBEROUS SCLEROSIS	7596
OTH SPEC SYND	7598
POTTER SYNDROME	Potter syndrome
MULT CONGEN ANOM UNSPEC	7599
DIAPHRAGMATIC HERNIA	S603

Table 7. Defect Groupings for Hypothesis Testing[a] — Continued

Category Title	Specific Defects Included[b]
OMPHALOCELE	S606, includes gastroschisis
OTHER NEOPLASM	S621
CYTOMEGALOVIRUS	S702
HERPES SIMPLEX	S704
SYPHILIS	S705

[a]Groupings of defects used in various tests of hypotheses.
[b]Modified ICD-8 codes except as noted.
[c]Any baby with two or more defects is considered to have "multiple" defects, except where a defect can be considered "secondary" to another, or where the defects are all in the same code group. See Table 8 for rules used to classify babies.
[d]Single codes 7461 (transposition of the great vessels) and 7462 (tetralogy of Fallot) are considered "complex" cardiovascular defects. Excludes babies who do not have at least one Category 1 cardiovascular defect.
[e]Excludes diagnoses of "possible," "probable," and "rule out."