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Final Report

Occupational Exposures and Selected Congenital Defects

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I. INTRODUCTION

Congenital heart disease is the most important form of heart disease in children in the United States, accounting for almost 90% of cardiac disease under age 15. The Collaborative Perinatal Project, a prospective study of pregnant women, found six to eight infants born with congenital heart disease for every 1,000 live births. Thus, in the United States alone, over 22,000 infants are born with congenital heart disease every year. About one third of these newborns will die during the first year of life. While improved surgical therapy over the last thirty years has reduced mortality in affected children, there is always a risk associated with surgery and an enormous life-time financial cost of continued cardiac monitoring and follow-up.

Clearly, prevention of congenital heart disease is desirable. To this end, several studies have been carried out with the purpose of identifying pre-natal factors associated with an increased risk of congenital heart disease. Most of these studies have examined the genetics of congenital heart disease, and the findings have led to two major conclusions: First, the genetic predisposition seems different for each specific cardiac lesion, and second, congenital heart disease appears to be a multifactorial disorder in which genetic factors may predispose to a lesion, but environmental factors are also important.

Historically, the search for environmental factors in the etiology of congenital heart defects is of fairly recent origin. Most clinicians and researchers up to the early 1900's were of the opinion that cardiac defects were caused mainly by hereditary factors. With the findings of Gregg and others that maternal rubella infection during pregnancy may cause congenital heart defects and other abnormalities, investigators began to explore the role of other viral infections during pregnancy in the study of congenital heart disease. The results have been inconclusive.

The thalidomide tragedy in Europe, where thousands of pregnant women ingested a sedative resulting in offspring with limb deformities, cardiac defects, and other malformations, highlighted the potential importance of chemical teratogenesis. In recent years, investigators have searched for a risk of heart defects with other maternal drug use in pregnancy, often with conflicting results. Thus, there appears to be a risk associated with female sex hormone use, but not for specific lesions such as the conotruncal malformations. Some studies have found a risk associated with emesis in pregnancy, others found a risk associated with the medications used for emesis. In some areas of research such as occupational exposures of parents, or geographic differences in rates of cardiac defects, there are no data available.

In summary, there is a dearth of information on possible risk factors of most of the cardiac defects. In fact, few studies have been done on environmental risk factors for specific cardiac lesions or related groups of lesions.

A study which is designed to explore the relationship of exposures in pregnancy to the risk of specific congenital heart defects might extend the range of variables associated with congenital heart disease and provide further clues to an explanation of the etiology.

The present study was designed primarily to investigate two major hypotheses: 1) that use of anti-nausea medication during pregnancy may be associated with the development of conotruncal malformations in the offspring, and 2) that possible parental occupational exposures to lead and other potential teratogens before and during pregnancy may increase the risk of a conotruncal malformation in the offspring. In order to study the role of these and other factors, a case-control study was conducted of children with the conotruncal malformations, tetralogy of Fallot and pulmonary stenosis who were born in the Baltimore SMSA from 1970 to 1976.

Any positive findings from this study would have significance in terms of further identifying possible risk factors in congenital heart defects. Moreover, the factors are potentially alterable so that preventive measures for congenital heart defects might be possible.

II. GENERAL DESIGN

The study was designed to compare exposures pre-pregnancy and during pregnancy among three groups of women: women who subsequently gave birth to children with conotruncal malformations, women who gave birth to children with Down's syndrome, and women who gave birth to children without either defect.

A case-control design was selected for this study because congenital heart disease is a fairly rare defect with estimated prevalence rates at birth varying from 5 to 8/1,000 and for conotruncal malformations from 0.8 to 1 per 1,000 births.

In general, the study proceeded as follows: Within a defined population, cases of conotruncal malformations were identified and normal controls were selected. A second set of controls consisting of children with Down's syndrome were also identified. Information on parental exposures before and during pregnancy with the child was obtained by mailed questionnaire and by telephone follow-up to the families. Additional information was obtained from birth certificates and medical records. Comparisons of the three groups were made to

determine if an association exists between exposures to certain drugs and occupational exposures and bearing a child with conotruncal malformations when confounding and effect-modifying factors are taken into account.

Details of each aspect of the study are discussed in the following sections.

III. SOURCE OF THE STUDY GROUPS

The defined population from which the study groups came consists of all children born alive between January 1, 1970 and December 31, 1976 to mothers living in the Baltimore Standard Metropolitan Statistical Area (SMSA). This area consists of Baltimore City, Anne Arundel, Howard, Carroll, Baltimore, and Harford Counties. During this time, 206,107 live births occurred, and these are the source for the three study groups (Table 3.1).

All births occurring in Maryland are recorded on birth certificates and filed with the Maryland State Office of Vital Records. Women who reside in the Baltimore SMSA but who give birth outside Maryland have certificates officially recorded in the state where the birth occurred, but copies of the certificate are sent to the Maryland county of residence. Regardless of whether the resident's birth is in or out of Maryland, information about the births is stored on computer tapes maintained by the Maryland Office of Vital Records.

TABLE 3.1

Live Births in the Baltimore Standard Metropolitan Area by County, 1970 to 1976[1]

County	YEAR						
	1970	1971	1972	1973	1974	1975	1976
Anne Arundel	5,1111	5,009	4,702	4,568	4,550	4,628	4,667
Baltimore City	16,068	15,070	13,265	11,794	11,284	11,280	11,199
Baltimore County	9,166	8,629	7,579	6,981	7,157	7,053	6,743
Carroll County	1,155	1,096	971	964	968	1,073	1,016
Harford County	2,241	2,218	2,003	1,951	1,968	1,875	1,984
Howard County	1,022	1,032	1,074	1,113	1,234	1,285	1,361
Total	34,763	33,054	29,594	27,371	27,161	27,194	26,970

(1) Source: Computer tape of births supplied by Maryland State Office of Vital Records

A. Definition and Ascertainment of Cases

Out of the defined population of 206,107 births, from 165 to 200 children were born with conotruncal malformations; the following lesions were selected for study:

1. Tetralogy of Fallot
2. Valvular or infundibular pulmonary stenosis with and without ventricular septial defect.

1. Criteria for Eligibility

The criteria for eligibility as a case in the study were the following:

a. Visual residence of the mother in the Baltimore SMSA at the time of birth (as determine by the birth certificate)
b. The child was not adopted
c. Documentation of the lesion was by one of the following sources:
    1. autopsy
    2. surgical record
    3. cardiac catheterization report. Catheterization evidence for pulmonic stenosis alone consisted of a resting peak systolic gradient between the right ventricle and pulmonary artery of at least 15 mm Hg.
    4. Clinical judgement by a board eligible pediatric cardiologist; made after the child is 6 weeks old

The justification for accepting a clinical judgement only after the child is six weeks old is based on findings that certain infants, primarily premature infants, may have findings suggestive of pulmonic stenosis at birth but the lesion spontaneously resolves by age six weeks. If the apparent pulmonic stenosis spontaneously resolved in an infant, that infant dose not have a congenital heart defect and therefore, would not be eligible for the study. If a pediatric cardiologist disgnosed pulmonic stenosis in a child after six weeks of age, the lesion was considered permanent and the child eligible as a case in the study.

Cases of pulmonary atresia and doublet outlet right ventricle were included since they represent severe forms of pulmonary stenosis and overriding aorta, characteristic of tetralogy of Fallot.

In some cases, a child had had conflicting diagnoses made by pediatric cardiologists at different times. In these cases, a pediatric cardiologist was asked to review the medical record and determine if the evidence was sufficient to diagnose the defect. Of 17 children who had conflicting diagnoses, 10 were excluded from the study because the diagnosis could not be established.

d. Child did not have any of the following conditions:

1. A chromosomal abnormality (e.g. Trisomy 21)
2. Noonan's syndrome (a genetic abnormality which includes pulmonic stenosis)
3. Congenital rubella
4. Single ventricle
5. Transposition of the great vessels
6. Isolated peripheral pulmosic stenosis

2. Sources of Cases

The cases were ascertained from eight sources. The sources were searched in the following order:

a. Cases enrolled in the Maryland Collaborative Birth Defect Study

b. The Pediatric Cardiology Center at The Johns Hopkins Hospital

c. The Pediatric Cardiology Center at the University of Maryland Hospital

d. Cardiac catheterization laboratory at The Johns Hopkins Hospital

e. Surgical files maintained by thoracic surgeons at the University of Maryland Hospital

f. Files on cardiac patients at Baltimore City Hospital and Sinai Hospital

g. Hospital summary diagnostic lists

h. The Pediatric Cardiology Center at Children's Hospital, District of Columbia

Each source for the cases is discussed more fully below.

The Maryland Collaborative Birth Defect Study was begun in 1975 to evaluate the effects of maternal hormone use in pregnancy on the risk of congenital heart defects in the offspring. Children born between January 1, 1972 and December 31, 1975 with transposition of the great vessels, tetralogy of Fallot, and pulmonic stenosis with ventricular septal defect were included. Children identified in that study who were eligible for the current study were included. A total of 33 cases were ascertained from this source.

The Pediatric Cardiology Center at The Johns Hopkins Hospital is one of two pediatric cardiology facilities in the State of Maryland, and until 1976, was the only one fully equipped to perform cardiac catheterization on young children. The Center has an automated data processing system in which patient data and visit information are stored. On June 1, 1978 a list was obtained of all children seen between January 1, 1970 and the date of the list request with a diagnosis of pulmonic stenosis, tetralogy of Fallot, and pulmonary atresia. A total of 77 additional cases were ascertained from this source.

The Pediatric Cardiology Center at the University of Maryland Hospital was established in September, 1976. Before then, consultations on children with cardiac problems were noted in the regular pediatric medical records, and infants were referred to Johns Hopkins for catheterization. After September 1976, medical records on all patients seen by the staff of pediatric cardiology were filed, alphabetically, at the Pediatric Cardioloyg Center. All records at the Center were searched in July, 1978 for cases meeting the criteria specified above. A total of 12 cases were ascertained from this source.

The staff at the catheterization laboratory at The Johns Hopkins Hospital maintains a record of all cardiac catheterizations done, the ages of the patients, and the diagnoses based on the catheterizations. The records from January 1, 1976 to June 30, 1978 only were available and searched for cases meeting study criteria. A total of 4 additional cases were ascertained from this source.

At University HOspital, thoracic surgeons perform cardiac surgery on pediatric patients. The patient's name, age, diagnosis, and date of surgery are recorded in a log book, which was searched for potential cases. A total of 5 additional cases were ascertained from this source.

Sinai Hospital and Baltimore City Hospitals have systems whereby cardiac patients, who have not necessarily been hospitalized, can be identified. File cards were maintained on clinic patients seen by the cardiologist; patients identified as potential participants were then further screened by review of their medical records. A total of 4 additional cases were ascertained from these sources.

The hospital summary diagnostic index lists were searched for new cases. The following hospitals participated in the study: Johns Hopkins, University Hospital, Church Home and Hospital, Anne Arundel County General, St. Agnes, Baltimore City Hospital, Bon Secours, Franklin Square, Greater Baltimore Medical Center, Lutheran, Maryland General, Mercy, Provident, St. Joseph's, Sinai, South Baltimore General, Union Memorial, Carroll County General and John F. Kennedy Institute. For each hospital, the summary hospital diagnostic index codes were searched from January 1970 to June 1978 for potential cases. Where possible, the search concentrated on the following H-ICDA codes:

1970-1973:	(7th edition of H-ICDA)
	746.2 (tetralogy)
	746.6 (valve anomaly)
	747.3 (pulmonary stenosis)
1974-1978:	(8th edition of H-ICDA)
	745.0 (tetralogy)
	745.7, .8 (pulmonary stenosis)

Children whose discharge diagnoses came under these codes still had to meet the eligibility requirements for participation.

In most hospitals, the diagnosis of congenital heart disease was imprecise and subsequently coded as 746.9 (unspecifed CHD) or 782.4 (murmur) in the 7th edition of H-ICDA, and 747.2 (other CHD) or 774.5 (murmur) in the 8th edition of H-ICDA. A systematic sample of patients with these codes was drawn and their records reviewed in order to estimate the yield of additional cases. There were no patients with these four codes who were subsequently included, so the effort to locate cases within these codes was discontinued.

Overall, three additional cases were ascertained after searching the hospital summary diagnostic index lists.

An attempt was made to locate cases who were born in the Baltimore SMSA, but may have been treated out of state. Therefore, a search for cases included Children's Hospital in Washington, D.C.

The staff in the Pediatric Cardiology Center at Children's Hospital sees cases from the Northern Virginia, Washington, D.C. and Southern Maryland areas. The medical records are arranged alphabetically and each one would have needed a review for diagnosis, date of birth, and address at birth. However, data on patients who have been catheterized were coded onto McBee cards for future studies, and could be retrieved by diagnostic code. As the yield from this source was expected to be small, a practical decision was made to review only patients who had been catheterized. The patients were selected according to the diagnostic codes for tetralogy of Fallot, pulmonic

stenosis with and without ventricular septal defects; selection was also based on birth dates between January 1, 1970 and December 31, 1976. On this basis, 161 patients were selected as potential cases. Attempts were made to locate these 161 birth certificates in the Maryland State Vital Records Office. If no birth certificate could be found, it was assume the child was not born in Maryland and thus not eligible for participation in the study.

A total of 2 cases from this source met the diagnostic criteria for eligibility and had birth certificates documenting maternal residence in the Baltimore SMSA.

3. Case Ascertainment

The final count of cases eligible for the study is shown in Table 3.2 The expected number of cases of these conotruncal malformations in the population varies depending on what estimate of the prevalence rate of these lesions per 1,000 live births is used in the calculations. Table 3.2 shows the range of expected numbers, with most of the variations due to differences in the diagnosis of pulmonary stenosis.

Generally, fewer cases than expected were ascertained. This was not intended to be a prevalence survey, so complete ascertainment was not a goal. The concern with ascertainment is the possible risk of selection bias in the cases finally included. Possible reasons for apparently incomplete ascertainment include the following:

TABLE 3.2

Expected Numbers of Conotruncal Cases Based on Prior Surveys of Prevalence Rates at Birth Compared to Observed Numbers of Cases

Studies Providing Estimates of Prevalence Rates at Birth	Tetralogy of Fallot		Pulmonic Stenosis	
	Rate (1)	Expected Number (2)	Rate (1)	Expected Number (2)
Mitchell, 1971	.29 .20	60 41	.75	156
Hoffman, 1978	.32	66	1.2	247
Czeizel, 1972	.42	87	.38	78
Feldt, 1971	.28	58	.28	58
Kenna, 1975	.26	54	.51	105
Carlgren, 1959	.26	54	.31	64
Observed Number of Cases	--	46	--	94

(1) Per 1,000 live births
(2) The rate is applied to the study population of 206,107 births in Baltimore SMSA

a. Out-migration of families, or births out of state

b. Lack of diagnoses by a pediatric cardiologist

c. Misclassification of cases

d. Overestimation of cases in previous research

e. Non-participation by two hospitals

Each possible reason is discussed more fully below.

One reason may be that families of cases migrated away before diagnosis. The 1970 census showed that approximately 3% per year of the population of the Baltimore SMSA migrated from their respective counties. However, over half of those moving from the city stayed within suburban Baltimore, while about 18% of the suburban migration was into the city limits. In order to estimate the magnitude of the migration problem, let us assume the following:

a. In each study year, 3% of the births left the Baltimore SMSA entirely.

b. Families of children with congenital heart defects left the area at the same rate and within a year of birth (i.e., prior to detection).

c. The rate of conotruncal malformations is 1.0 per 1,000 live births.

A maximum estimated loss to migration is shown on Table 3.3, about six cases.

Some cases, particularly those from the out-of-state hospital, could have been lost if the parents lived in the Baltimore SMSA but the

TABLE 3.3

Estimated Loss of Cases Due to Migration of Families
Prior to Detection

Year	(1) Number of births	(2) Assumed annual outmigration	(3) Estimated rate of heart defects	(1)X(2)X(3) # of cases lost to migration
1970	34,763	.03	.001	1.04
1971	33,054	.03	.001	.99
1972	29,594	.03	.001	.89
1973	27,371	.03	.001	.82
1974	27,161	.03	.001	.81
1975	27,194	.03	.001	.82
1976	26,970	.03	.001	.81
Total				≈6

child had been born outside the state. In order to estimate the potential seriousness of this problem, a calculation of the number of cases missed was done as follows:

a. Only 0.8% of births to Maryland residents occur outside the state, with 89% of these births occurring in the District of Columbia.

b. If one assumes the rate of conotruncal malformations is 0.8 per 1,000 live births, then the loss is: (% births out-of-state) X (% of out-of-state births in District of Columbia) X (rate of conotruncal malformations) X (number of births) = (0.8%) (89%) (.1%) (206,107) = 1.2 cases.

Cases may also have been lost if they had been detected by a physician but not referred to a pediatric cardiologist. Since in this study, the definition of a case required confirmation by a pediatric cardiologist, some cases may not have been included. For mild cases of pulmonary valve stenosis, this possibility was likely. To estimate the problem, a survey was done of 20 children who were seen at The Johns Hopkins Pediatric Emergency Room or Comprehensive Clinic and diagnosed as having pulmonary stenosis. Johns Hopkins has the largest pediatric cardiology center in Maryland and cardiac consultations are available in the clinic. Nonetheless, 10 of the 20 children were not known to any pediatric cardiologist; the other ten were known at either Hopkins or University of Maryland. All ten of the unknown cases were at one time diagnosed with peripheral pulmonic stenosis, and all had a series

of visits with the murmur heard in some visits and not in others. There is no obvious way to estimate the number of cases which might have been missed because no referral to a pediatric cardiologist was made.

Cases may not have been ascertained because of misdiagnosis. In particular, differentiating clinically mild pulmonic stenosis without a pulmonic click from atrial septal defect can be difficult. When both diagnosis were in the medical record, the case was not included unless pulmonic stenosis was subsequently determined by catherization, surgery, or on further follow-up, the cardiologist determined the murmur was due to pulmonic stenosis. Some cases labeled atrial septal defect who had no subsequent follow-up might in fact have been cases of pulmonic stenosis. The extent to which misclassification resulted in a loss of cases is unknown.

Another possible reason that fewer cases were ascertained than expected is that expected rates were based on previous research studies which may have overestimated the prevalence rate per live births of these malformations. As discussed previously, occasionally infants, particularly premature infants, are diagnosed with apparent pulmonic stenosis which tends to disappear by age six weeks. Therefore, prevalence studies for pulmonic stenosis of the structural variety should state whether the diagnosis was made after age six weeks. The studies quoted in Table 3.2 are difficult to assess in this regard because distribution of dates of diagnosis by lesion are not specified, and in two studies, cases of peripheral pulmonic stenosis are not separated from pulmonary valve stenosis.

Cases may also have been missed because of non-participation by two hospitals in the Baltimore SMSA, Howard County Hospital and Harford Memorial. However, the number may be negligible for the following reasons:

a. The chief of pediatrics at Harford Memorial informed us that all severe cases born there are referred to Johns Hopkins. Furthermore, a survey of the diagnostic indexes for the codes of interest revealed no cases.

b. Howard County Hospital did not begin operation until July, 1974, virtually 2/3 of the way through the study period. However, the Columbia Medical Plan, a pre-paid group practice serving Howard County, has been operating since 1970. While all cardiac referrals are made to Johns Hopkins from the Plan, it is conceivable that mild cases were not referred. The chief of pediatrics for the Columbia Medical plan estimated perhaps 2 or 3 pulmonary stenosis cases are currently in the entire practice.

Table 3.4 shows the prevalence rates by county. As expected, the rate was low for Howard County.

In addition, physicians in Anne Arundel County and Howard County refer cases to hospitals in the Washington, D.C. area. As discussed earlier, locating cases at one such hospital, Children's Hospital, could only be accomplished on the basis of catheterization reports. A total of 2 cases were located, but conceivably more cases diagnosed on clinical grounds would be missed.

TABLE 3.4

Prevalence Rates by County for Conotruncal Malformations

County	Number of Live Births	Case Ascertained	Rate/10,000
Anne Arundel County	33235	18	5.4
Baltimore City	89960	64	7.1
Baltimore County	53304	38	7.1
Carroll County	7243	7	9.7
Harford County	14240	9	6.3
Howard County	8121	4	4.9

The high prevalence rate in Carroll County was surprising, because some cases were presumably not located because of referral to Pennsylvania Hospitals. The rate may reflect the relatively small numbers of births for that county.

B. Definition and Ascertainment of Random Sample Controls

The second group studied in this project was labeled the "randon sample control" group. This control was defined as a child born alive between January 1, 1970 and December 31, 1976 to a woman residing in the Baltimore SMSA. Children were excluded from the random sample control group if they were adopted or if they had Down's syndrome, in which case the child was placed in the Down's syndrome control group.

1. Selection of Controls

The controls were selected from the birth certificate tape described previously to represent a random sample, stratified by hospital and year of birth, of the population of births from 1970 to 1976.

In general, all births on tape were stratified by year of birth, then by hospital of birth, then listed in random number order. For all cases of conotruncal malformations born within a certain year and hospital strata, three times as many control births were selected from that stratum.

Replacement controls were selected to insure that at the time of mailing the questionnaires, there were three times as many controls as cases from the same year-hospital strata. Reasons for selecting a replacement control were the following:

a. In the event a physician refused permission to include a control family, another control was selected.

b. If all tracing methods failed to locate the family, another control was selected.

The use of replacement controls introduced potential bias in favor of controls who were less mobile, had telephone numbers, and had driver's licenses (tracing methods to be discussed later, used telephone books and driver's licenses). This bias will be discussed further in the section on nonparticipation.

C. Definition and Ascertainment of Down's Syndrome Control

The third study group in this project was comprised of children born with Down's syndrome.

1. Criteria for Eligibility

The criteria for eligibility as a Down's Syndrome Control in the study were the following:

a. Usual residence of the mother was in the Baltimore SMSA at the time of birth

b. The child was not adopted

c. Documentation of Down's syndrome was by one of the following sources:

1. The chromosome analyses demonstrated either Trisomy 21, translocation for part of 21, or mosaic 46/47 for 21.
2. The child's medical record noted any six of the stigmata of Down's syndrome shown in Table 3.5.
3. A statement by the private pediatrician to our study group that the child under his care had Down's syndrome.

The criterion stating at least six physical findings had to be in the medical record was based on criteria used in a previous study of Down's children in the Baltimore area. The selection of the number six was, in that study and in this one, arbitrary.

The inclusion of children based on a private pediatrician's statement reflected the fact that although the medical record may not contain six physical findings, there were children being followed by private pediatricians for clinical problems with Down's syndrome well past the child's infancy. The decision was made to include these children if the pediatrician would attest to the diagnosis.

In this study, five children suspected at birth of having Down's syndrome were not inlcuded because the data were insufficient to classify them as Down's syndrome.

TABLE 3.5

Physical Findings Used in the Criteria for Eligibility in the Down's Syndrome Control Group(1)

Brachycephaly

Slanted Palpebral fissures

Epicanthal folds

Palmar simean crease

Malformed ears

Broad and/or short neck

Malformed fingers and/or hands

Nasal abnormality

Hypertelorism

Abnormal palate

Brushfield Spots

Broad and/or short trunk

Mental retardation

Congenital heart disease

Abnormal hip angles

(1) Any six of these fifteen findings were sufficient to include child as Down's Syndrome control.

2. Sources of Down's Syndrome Controls

Down's syndrome controls were ascertained from the following sources, in the order listed.

a. Pediatric Cardiology Center at University of Maryland Hospital and The Johns Hopkins Hospital.

b. Genetic counseling service at Sinai Hospital.

c. Chromosome analyses laboratory at the John F. Kennedy Institute.

d. Medical records at the John F. Kennedy Institute.

e. Hospital Summary Diagnostic list.

f. Genetics clinic at The Johns Hopkins Hospital.

g. Chromosome analyses laboratory at Greater Baltimore Medical Center.

h. Down's syndrome parents' group.

As each source had its unique features for ascertainment, each is discussed more fully below.

When ascertaining Down's syndrome controls from the Pediatric Cardiology Units at Johns Hopkins and University Hospitals, exactly the same procedures described for selection of cases were used. A total of 13 Down's syndrome controls were ascertained from these sources.

Sinai Hospital has operated a chromosome analyses laboratory and genetic counseling service since 1968. Cases are referred from the Sinai nursery, pediatric clinic and private physicians. A total of 55 additional Down's syndrome children were ascertained from this source.

Down's syndrome controls were ascertained from files maintained at the chromosome analyses laboratory in the John F. Kennedy Institute. The laboratory staff received requests for analyses from several physicians in the Baltimore area. A total of 35 additional Down's syndrome controls were ascertained from this source.

The medical record administrator for the John F. Kennedy Institute keeps a record of all inpatient children diagnosed with Down's syndrome (H-ICDA Code 759.3). The administrator has also attempted to keep a list of outpatient Down's syndrome children, but the list is not complete and represents only the children whose records were requested on days when she worked. Nevertheless, both sources were used to identify cases of Down's syndrome not previously found. A total of 5 additional cases were identified from this source.

A procedure identical to that undertaken for the cases was done to identify Down's syndrome children from Hospital Summary Diagnostic Lists. The H-ICDA code for Down's syndrome is 759.3 and has remained constant for all years of the study. A total of 46 additional Down's syndrome children were ascertained from these sources.

The staff at the genetics clinic at The Johns Hopkins Hospital maintains medical records in alphabetical order of all patients they have counseled for genetic disorders. All medical records for the clinic were searched for Down's syndrome controls meeting study criteria. A total of 3 additional cases were ascertained.

A total of 1 additional case was ascertained from the chromosome laboratory at Greater Baltimore Medical Center.

The last source was a Down's syndrome parents' organization in Anne Arundel County. Most of the parents had already been located using other sources. However, two families in the group had not been contacted and wished to participate, and they were included.

It was not expected that the Down's syndrome children ascertained from these sources were all or even representative of all of the Down's syndrome children born in the Baltimore SMSA during January 1, 1970 to December 31, 1976. The primary purpose of these controls was to attempt to monitor the problem of differential recall of certain questionnaire items from mothers of children with birth defects. For this purpose, it was desirable to include children with degrees of severity of Down's syndrome ranging from mild manifestations to terminal illness. Thus, the parents of this group will have as similar a range of experiences with a defective child as possible to that of parents of the congenital heart disease cases.

3. Ascertainment of Down's Syndrome Controls

Even though complete ascertainment of Down's syndrome children was not a goal of this study, it is important to note any selection biases in ascertainment that may limit the usefulness of this group to control for recall bias.

The expected numbers of Down's syndrome controls in the population varies depending on which rates are used. Table 3.6 illustrates the numbers obtained from seven rates, which are among the few that provide maternal age-specific rates and represent the most recent data.

TABLE 3.6

Expected Numbers of Down's Syndrome Controls Based on Prior Surveys of Prevalence Rates at Birth Compared to Observed Numbers of Controls

Maternal Age	(A) Studies Providing Maternal Age-Specific Prevalence Rates at Birth[1]							(B) Births in each age group in BSMSA for 1970-76	(C) Range of Expected Numbers (A X B)=(C)
	Coleman Stoller	Jones Lowry	Mikkelsin	Lindsjo	Harlap	Zarfas Wolf	Hook		
15-19	.42	.80	.99	.59	1.1	.62	.68	42,349	18-46
20-24	.62	.55	.70	.74	0.7	.60	.66	69,881	38-52
25-29	.82	.77	.73	.88	1.5	.63	.79	59,702	38-89
30-34	1.14	1.11	1.71	1.45	2.2	1.12	1.26	23,941	27-53
35-39	3.45	3.23	3.04	3.74	5.8	3.40	3.73	7,218	22-42
40-44	9.80	12.51	14.61	14.96	18.0	3.69	13.16	1,640	6-25
45+	21.68	24.31	10.75	62.09	17.3	47.30	35.25	92	1-6
									Total 150-313
									Observed 160

(1) Per 1,000 live births

There were fewer Down's syndrome children than were expected based on prior reserach figures. In addition to reasons cited previously for the cases, another reason for the deficit was a decision not to pursue cases through the school system and through private pediatricians. These sources would individually require significant investments of time to contact and yield only a few cases for each source. The Down's syndrome children known only through these sources were missed, but as complete ascertainment was not intended, it was felt these sources would be the least productive.

The prevalence rate of those ascertained by county are shown in Table 3.7. The low rate in Harford and Anne Arundel counties are probably due in part to non-participation by the hospitals and out-of-state referrals, as discussed previously under cases.

The low prevalence rate in Carroll County may reflect a combination of (1) out-of-state referrals, (2) private physician management of children, (3) a practice of seldom ordering chromosome analyses, (4) not noting Down's syndrome in hospital medical records. There are no data to determine which of these factors is the more likely explanation.

Except for Carroll County, the counties with different levels of ascertainment for cases and Down's syndrome controls are the same.

In terms of comparability of ascertainment by county, there appeared to be no important differences between cases and Down's syndrome controls.

TABLE 3.7

Prevalence Rates by County For Down's Syndrome Controls

County	Number of Live Births	Down's Syndrome Ascertained	Rate/10,000
Anne Arundel County	33235	21	6.3
Baltimore City	89960	70	7.8
Baltimore County	53304	54	10.1
Carroll County	7243	1	1.4
Harford County	14240	10	7.0
Howard County	8121	4	4.9

IV. TRACING STUDY PARTICIPANTS

Tracing involved the following efforts, and no case or control was considered untraceable until all these steps had proven fruitless:

1. Address obtained from medical record of the hospital as of the last known visit.
2. Address verified or updated from current phone book listing under married name or maiden name of the mother. If there was no phone listing, directory assistance was called to see if the number for that name at that address was unlisted. If so, the questionnaire was mailed under the supposition that the address was correct, although no phone was listed.
3. The Stewart's Directory was used. This directory has identical information to that in the telephone directory, but names and telephone numbers are organized by street address, in one section, and telephone number in another section. The Stewart's Directory was consulted to obtain addresses and phone numbers of neighbors who might have additional information.
4. The Maryland Department of Motor Vehicles provided a computer listing of names and addresses of residents who have a Maryland driver's license.
5. If the child was of school age, the school records kept by the Baltimore City Department of Education, Center for Planning, Research and Evaluation were reviewed for the child's current address as of the school year.

V. METHODS OF DATA COLLECTION

Data for this study came from three sources: Birth certificates, mailed questionnaires with telephone follow-up, and medical records. Each source is discussed more fully below.

A. Birth Certificates

Birth certificates on all the children in the study were reviewed for the following information.

1. Name
2. Mother's and father's name
3. Address
4. Date of Birth
5. Hospital of Birth
6. Birthweight
7. Race of child and parents
8. Sex
9. Age of mother
10. Usual residence of mother
11. Name and address of attending physician
12. Presence or absence of malformations
13. Maternal pregnancy history
14. Date of last menstrual period

The data were copied onto a standard form (Appendix 3).

B. Mailed Questionnaire and Telephone Follow-Up

A self-administered questionnaire was devised to obtain information from the mother about the pregnancy with the study child. A prelimiary questionniare was pretested in six women who had children from two to twenty years ago. After the pre-test, the questionnaire was modified to clarify ambiguous questions and a final version was prepared. Specific questions cover the following areas:

1. Type of response
2. Respondent (mother/other)
3. Maternal age, weight and height
4. Paternal age
5. Use of estrogens and progestins before and during pregnancy, and reason for use
6. Difficulties in conceiving
7. Difficulties in pregnancy (bleeding, etc.)
8. Method of testing for pregnancy
9. Nausea or vomiting with pregnancy and use of anti-nauseants
10. Sleeplessness, depression, and other problems and use of anti-anxiety agents before and during pregnancy
11. Occupational history of mother and father before and during pregnancy (possible lead, anesthesia, cleanser exposure)
12. Occupational history of any other adult living with the mother before and during pregnancy
13. Maternal history of diabetes, thyroid dysfunction, phlebitis, kidney disease, and uterine dysfunction

14. History of maternal smoking and alcohol use before and during pregnancy

15. Fertility history

The sequence of events involved in mailing the questionnaire was as follows. First, permission to contact the family was obtained from the hospital and individual physician. If the physician was no longer in Maryland, permission was sought from the Chief of Service at the hospital. Second, extensive tracing was undertaken as described to locate the family. Finally, the questionnaire was mailed with an appropriate cover letter explaining the study. For those participants who did not respond within four weeks of mailing the questionnaire, a telelphone follow-up was attempted.

Telephone interviews were arranged to supplement the mailed, self-administered questionnaire. Three telephone interviewers were trained, two initially and one as a replacement. Each interviewer was instructed on how to administer the questionnaire over the phone, and actual interviews commenced only after the interviewer had practiced with at least three individuals. In situations where no telephone number was available, a second and if necessary, third mailing was done. In 33 instances, a personal interview was arranged where the respondent could not read or no phone was available.

In over 98% of the completed questionnaires, the mother of the study child was the respondent. (Table 3.8) The primary reason that another person responded was the death of the mother.

TABLE 3.8

Number and Percent Distribution of Participating Cases and Controls by Type of Respondent

	Total		Cases		Random Controls		Down's Controls	
Respondent	No.	%	No.	%	No.	%	No.	%
Mother	565	99.0%	113	96.6%	332	99.4%	120	100%
Father	5	0.9%	3	2.6%	2	0.6%	0	--
Other	1	0.1%	1	0.8%	0	--	0	--
TOTAL	571		117		334		120	

C. Hospital Medical Records for Cases and Down's Controls

The medical records were carefully reviewed for the cases and Down's controls, and information relevant to the study abstracted. The following information was collected:

1. Name, address, and phone number
2. History number
3. Status of the child (dead/alive) at discharge
4. Physician
5. Pre-natal history
6. Hospital of birth
7. Date of birth
8. Race
9 Sex
10. Birthweight
11. Maternal age
12. Source of the case or Down's child (cardiology unit, discharge abstract, etc.)

The following additional information was collected for cases:

1. Type of cardiac lesions (tetralogy, pulmonary stenosis)
2. Diagnostic certainty of the cardiac lesion

The following additional information was collected for Down's controls.

1. Method of diagnosing Down's syndrome (chromosomes/clinical)
2. Type of cardiac lesions, if any, and diagnostic certainty of the lesion.

VI. NON-PARTICIPATION

Reasons for failure to complete the questionnaire include:

1. Physician refusal to allow participation
2. Subject not traceable (using procedures discussed previously)
3. Subject refusal to participate

Figures 3.1 to 3.3 show the composition of cases, random sample controls, and Down's syndrome controls after hospital and physician refusals were obtained.

Of the total number of eligible participants, completed questionnaires were obtained from 84% of the cases, 72% of random controls, and 74% of Down's controls. (Table 3.9) The main reason for non-participation was inability to locate the family. Only four physicians refused to allow participation, and their refusal limited access to 6 controls and one Down's child. Subject refusal was defined both as a definite statement of refusal to the project staff, and as a non-response to three mailings where telephone contact was not possible. Table 3.10 shows that among those eligible to participate and who were traced, the refusal rate is similar for cases and normal controls.

Comparisons between participants and non-participants was done to uncover any potential bias in response. The results are presented for each study group.

A. Participation Among Cases

For purposes of the following tables, the category of tetralogy of Fallot also includes cases of pulmonary stenosis with ventricular

Figure 3.1

Flow Chart of the Selection and Exclusion of Cases of Conotruncal Malformations

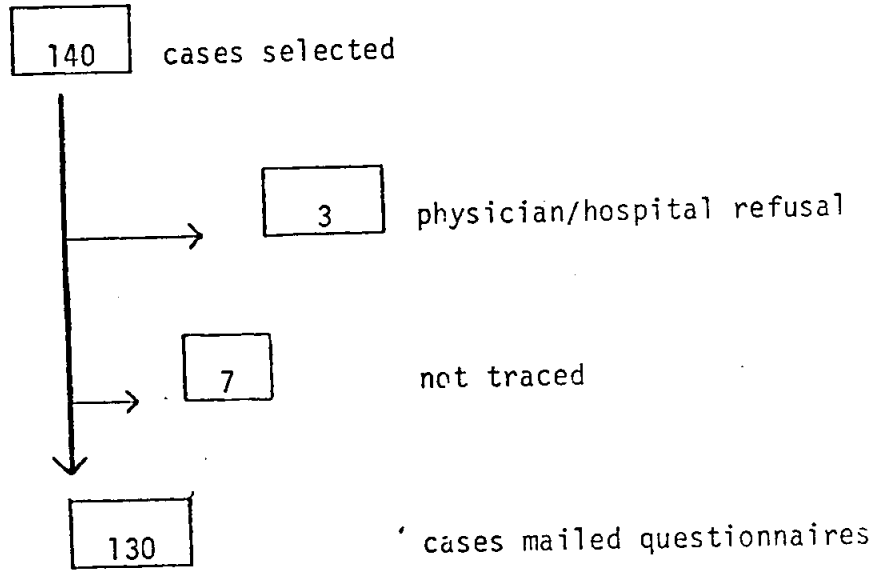

Figure 3.2

Flow Chart of the Selection and Replacement of Random Sample Control

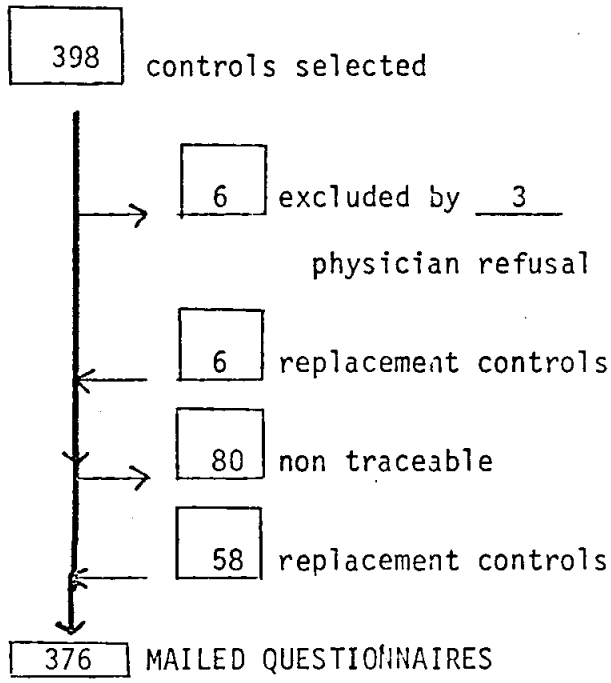

Figure 3

Flow Chart of the Selection and Exclusion of Down's Syndrome Controls

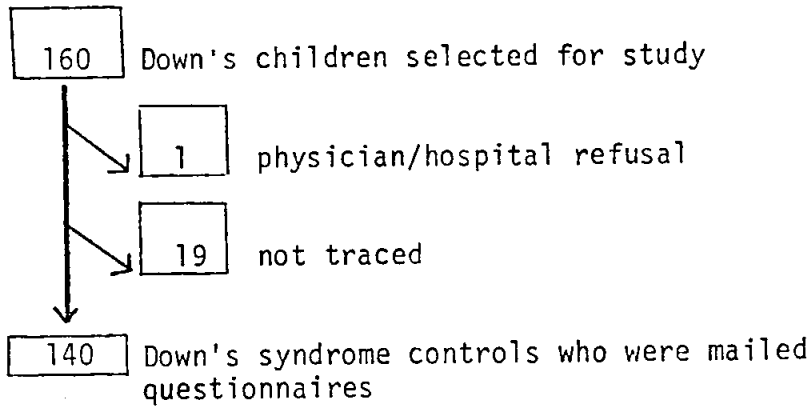

TABLE 3.9

Number and Percent Distribution of Cases and Controls
by Status of Participation and Reason
For Non- Participation

Response	Total		Cases		Random Controls		Down's Controls	
	No.	%	No.	%	No.	%	No.	%
Participation	571	75%	117	84%	334	72%	120	75%
Non-participation								
Hospital/physician refusal	10	1%	3	2%	6	1%	1	1%
Subject Refusal	75	10%	13	9%	42	9%	20	12%
Not Traced	106	14%	7	5%	80	17%	19	12%
Total	192	25%	23	16%	128	27%	40	25%
Total	763		140		462		160	

TABLE 3.10

Refusal Rates for Case and Controls
Who Received Questionnaires

Number	Cases	Random Controls	Down's Controls
Eligible	130	376	140
Number Refused	13	42	20
% Refusal	10%	11%	14%

septal defect. The category of pulmonary stenosis includes pulmonary valve or infundibuler stenosis alone, with atrial septal defect, with ventricular septal defect plus another defect (other than overriding aorta), and pulmonary atresia.

The same percentage of cases participated within each diagnostic category (Table 3.11). However, slightly more families of tetralogy cases refused to participate, and slightly more families of pulmonary stenosis cases were not contacted (either not traced or physician refusal).

Most of the cases were dignosed by catheterization, surgery, or autopsy, as shown by Table 3.12, attesting to the high level of certainty about the diagnoses of the cases. Of the 40 cases (29%) diagnosed on clinical grounds alone, the majority were pulmonary stenosis. As Table 3.13 shows, there was no evidence of a pattern in level of participation by any diagnostic procedure.

The percent of participation by counties are shown on Table 3.14. The participation rates were lowest in Carroll and Howard County, in part reflecting the small number of cases ascertained.

B. Participation Among Down's Syndrome Controls

Figure 3.2 demonstrates the final composition of Down's syndrome controls after hospital and physician refusals were obtained.

As shown in Table 3.15 the proportion of Down's syndrome controls participating in the study was higher among those with no cardiac defect. With each group, Down's syndrome with and without cardiac

TABLE 3.11

Participant Status by Type of Conotruncal Malformation

Lesion	Total		Participants		Refusals		Not Contacted	
			Number	%	Number	%	Number	%
Tetralogy of Fallot	56	100%	47	84%	6	11%	3	5%
Pulmonary Stenosis	84	100%	70	83%	7	8%	7	8%
Total	140	100%	117	83.6%	13	9.3%	10	7.1%

TABLE 3.12

Level of Diagnostic Certainty Among Conotruncal Cases

Lesion	Total		Clinical		Catheterization		Surgery		Autopsy	
	No.	%	No.	%	No.	%	No.	%	No.	%
Tetralogy of Fallot	56	100%	9	9%	11	20%	37	66%	3	5%
Pulmonary Stenosis	84	100%	35	42%	8	10%	29	35%	12	14%
Total	140	100%	40	29%	19	14%	66	47%	15	11%

TABLE 3.13

Participant Status by Level of Diagnostic Certainty
For Conotruncal Malformations

Level	Total		Participant		Refusals		Not Contacted	
	No.	%	No.	%	No.	%	No.	%
Clinical	40	100%	32	80%	5	12.5%	3	7.5%
Catheterization	19	100%	17	89%	2	11%	--	
Surgery	66	100%	54	82%	6	9%	6	9%
Autopsy	15	100%	14	93%	--		1	7%

TABLE 3.14

Participant Status by County for Conotruncal Malformations

County	Total	Participants	
		Number	%
Anne Arundel County	18	16	89%
Baltimore City	64	54	84%
Baltimore County	38	31	82%
Carroll County	7	5	71%
Harford County	9	8	89%
Howard County	4	3	75%

TABLE 3.15

Participant Status by Cardiac Status
Among Down's Syndrome Controls

Lesion	Total		Participants		Refusals		Not Contacted	
	No.	%	No.	%	No.	%	No.	%
Pulmonary Stenosis	1	100%	1	100%	--		--	
Tetralogy of Fallot	3	100%	2	67%	1	33%	--	
Septal Defect	22	100%	13	59%	4	18%	5	23%
Other	27	100%	20	74%	4	15%	3	11%
Defect, type unknown	12	100%	9	75%	2	17%	1	8%
All Cardiac Defects	65	100%	45	69%	11	17%	9	14%
No Cardiac Defects	95	100%	75	78%	10	11%	10	11%
Total	160	100%	120	75%	21	13%	19	12%

defects, there was no difference in the proportion refusing and the proportion not contacted.

About half the cardiac defects among the Down's controls were diagnosed on clinical grounds only. Participation rates by level of diagnostic certainty did not seem to vary, although the numbers in each level were fairly small. (Table 3.16)

The percent of participation for Down's syndrome by county in this study are shown on Table 3.17. The participation rates were lowest in Baltimore City and Harford County. Participation by City residents was low because the families were difficult to locate and the refusal rate was higher.

C. Characteristics of Participants and Non-Participants

Data obtained from birth certificates were used to compare characteristics of participants among all three study groups in order to see if any biases among the three groups exist. Table 3.18 presents the results of the comparisons.

In all three groups, the non-participating mothers tended to be young, black and residing in Baltimore City, a group which was very difficult to trace to a current address.

Participation rates were lower among families of children born in the early study years, regardless of study group. The reasons were because of tracing difficulty and a higher refusal rate.

Among cases and Down's syndrome controls, non-participation was greater among families of deceased children. Few random sample controls included deceased children.

TABLE 3.16

Participant Status by Level of Diagnostic Certainty
Among Down's Syndrome Controls

Level	Total		Participants		Refusals		Not Contacted	
	No.	%	No.	%	No.	%	No.	%
Clinical	33	100%	22	67%	7	21%	4	12%
Catheterization	12	100%	7	58%	3	25%	2	17%
Surgery	12	100%	8	67%	2	17%	2	17%
Autopsy	8	100%	8	100%	--		--	

TABLE 3.17

Participant Status by County for Down's Syndrome

County	Total	Participants	
		No.	%
Anne Arundel County	21	17	81%
Baltimore City	70	45	64%
Baltimore County	54	47	87%
Carroll County	1	1	100%
Harford County	10	6	60%
Howard County	4	4	100%

TABLE 3.18

Selected Variables for Participants (P) and Non-Participants (NP) Among Cases and Controls

	Cases			Random Sample Controls			Down's Syndrome Controls		
ariables	Participants (N=117)	Refusals (N=13)	Not Traced (N=10)	Participants (N=334)	Refusals (N=42)	Not Traced (N=86)	Participants (N=120)	Refusals (N=21)	Not Traced (N=19)
ge of Mother									
≤20	24%	23%	30%	24%	40%	33%	15%	19%	26%
21-30	61%	62%	60%	64%	52%	63%	42%	38%	37%
30+	14%	15%	10%	12%	7%	5%	43%	43%	37%
ace of Child									
Black	18%	46%	30%	23%	40%	50%	25%	29%	37%
ounty of Residence									
Baltimore City	46%	39%	50%	43%	67%	66%	38%	52%	74%
Baltimore County	26%	46%	10%	28%	14%	19%	39%	24%	11%
Other	27%	15%	40%	30%	19%	15%	23%	24%	16%
Birthweight									
2500 gms +	76%	92%	70%	94%	90%	83%	82%	76%	79%
Birthdate									
1970-1971	27%	23%	20%	26%	29%	31%	26%	38%	42%
1972-1973	21%	46%	50%	25%	38%	23%	33%	33%	16%
1974-1975	38%	8%	20%	33%	29%	30%	23%	24%	37%
1976	15%	23%	10%	16%	5%	15%	18%	5%	5%
Status of Child									
Dead	21%	62%	30%	1%	0	1%	17%	29%	37%

The only difference among the three study groups appears to be in participation status by proportion of children with low birthweight. Overall, among non-participants, 22% of cases weighed under 2500 grams, compared to 9% of random sample controls and 19% of Down's syndrome controls; among participants, the proportion was 24% versus 6% versus 18%.

In general, participation rates for those mailed questionnaires were equal in all study groups. Among cases and Down's syndrome controls participation was lower among families with deceased children. The one difference among the study groups was the higher non-participation level among mothers of normal control children born weighing under 2500 grams.

VII. DATA PROCESSING

The data was coded by two trained clerks and checked by the author. The coded data were then transferred to IBM cards, punching and verification being carried out in the Data Processing Unit of the Department of Epidemiology of The Johns Hopkins School of Hygiene and Public Health. The information contained in the cards was then transferred to magnetic tapes in the IBM-360 computer. Internal consistency and validity programs were used to identify coding errors, which were then corrected.

VIII. DATA ANALYSES

Several data analytic approaches are used in conformity with the methods of control selection used. The main features of the control selection which had to be accomodated are the following:

(1) The random sample controls were a highly stratified random sample of the population of births in the Baltimore SMSA during the period 1970 to 1976. The strata consisted of each hospital of birth and each birth year, resulting in 133 possible strata.

(2) Within each stratum, three times the number of controls were selected as cases.

(3) The number of participating cases falling into the 133 strata varied from zero (55 out of 133) up to 5 (1 out of 133).

(4) In some instances, absence of satisfactory responses to individual questionnaire items for a case resulted in a stratum containing responses from controls only.

(5) The Down's syndrome controls were selected without regard to characteristics of the cases.

In order to assess the consequences of these design features on inferences drawn from the data collected, it was decided to pursue four approaches to the data analyses:

(1) An unmatched analysis comparing cases and both types of controls disregarding the stratification.

(2) A maximum likelihood analysis comparing cases and random sample controls which estimates odds ratios for risk factors by directly modelling each stratum effect. This procedure requires that strata without any cases be eliminated from consideration.

(3) A conventional matched set analysis for cases and random sample controls. This required that for strata containing more than one case, the controls be arbitrarily assigned to cases. Absence of data on any case in the matched set required the elimination of the set.

(4) A multivariate analysis using a logistic model which estimates odds ratios for risk factors while adjusting for possible confounding variables.

Each approach is discussed more fully below.

A. Unmatched Analyses

Frequency distributions of the major study variables for cases, random sample controls, and Down's syndrome controls were examined to identify variables which may be risk factors for CHD, and to see if there are variables which may show evidence of recall bias, as discussed earlier. If a difference in the frequency of a variable between cases and random sample controls was noted, the variable was examined for Down's syndrome controls. Evidence for bias of recall among case mother responses to a questionnaire item was considered if: 1) the comparison of the frequency distribution of responses for cases and random sample controls suggests a positive association of the variable with cases, and 2) the same comparison for Down's syndrome controls and random sample controls suggests a positive association of the variable with Down's syndrome controls. If both conditions are met, then recall bias could be at least part of the explanation for the positive association among the cases.

Conversely, evidence of no recall bias among case mothers responses to a questionnaire item consisted of a positive association of the variable with the cases compared to both sets of controls, or a similar frequency distribution of the variable among all study groups.

Chi square tests with Yates' correction for continuity were done to study the significance of the difference in frequency distributions. Whenever observed proportions were less than 25%, a logit transformation of the data was used and differences assessed with a Z test.

Whenever a difference is discovered between the Down's syndrome controls and the other two groups, the possibility that maternal age could be responsible for it was examined by using a 3-variable tabulation to hold constant the maternal age effects. It is important to control for the effects of materanl age since the Down's syndrome mothers were markedly older than the mothers in the other two groups.

This analytic approach which ignores the stratification in the design may be less sensitive than an analyses which considers strata effects. However, the purpose of this preliminary unmatched analyses is to identify variables which may be risk factors, and determine if differences could be due to recall bias.

B. Stratified Analyses

For this analysis cases and controls are allocated to hospital of birth-birth year strata. Each potential risk factor variable is dichotomized and tabulated by the strata for cases and each type of control. Maximum likelihood estimates of the common odds ratios are

calculated using a procedure that adjusts for variations in the frequency of the risk factor across stratum. This method assumes a logistic model for strata effects and the common odds ratio.

The statistical significance of the estimated odds ratio is assessed by means of the Likelihood Ratio test. In essence, this test relies on the fact that -2 log (L) has a chi square distribution with one degree of freedom; L is the ratio of the likelihood of the data evaluated for odds ratio = 1 to the likelihood evaluated at the odds ratio which maximizes it. A comparison of the maximum likelihood estimate of the common odds ratio and significance levels with the more familiar Mantel-Haenszel summary odds ratio procedure is presented.

C. Matched Analyses

The strategy for control selection was to take a random sample of births from the hospital-year strata selecting three times as many controls as cases in each strata containing at least one case. In practice, many strata contained only a single case and it controls which can be viewed as a matched set. Strata with multiple cases require arbitrary assignment of the controls to each case. It was decided that a matched set analyses should be undertaken and contrasted with the stratified analyses to assess the gain in precision from the full stratified approach.

Since the matched sets are a special case of the stratified sample with the number of "strata" equal to the numbers of case-control

sets, the maximum likelihood procedure depicted above for the stratified analysis may be applied here.

D. Multivariate Analyses

This analysis is based on a binary logistic regression model for relating the probability of a specific binary variable to a set of regressor variables. The model is as follows:

$$E(Y) = 1 \Pr(Y=1) + 0 \Pr(Y=0) \qquad (1)$$

$$= \Pr(Y=1)$$

$$= \frac{\exp(Bo + B_1 X_1 + B_2 t \ldots . B_k X_k)}{(1 + \exp(Bo + B_1 X_1 + B_2 X_2 + \ldots . (B_k X_k)} \qquad (2)$$

where

Y is the risk factor variable

B's are estimated regression coefficients

X's are independent variables (including case-control status)

K = number of regression coefficients

Prentice proposed a related model which leads to direct estimation of the odds ratio associated with exposure, and of the dependence of the odds ratio on other explanatory variables. He assumes the effects of confounding variables are identical for cases and controls; let us set up the probability of exposure as follows:

Let P_1 = probability of exposure for cases; $Q_1 = 1-P_1$

P_2 = probability of exposure for controls; $Q_2 = 1-P_2$

X_1 = 1 if an individual is a case

$X_2 = 2$ if an individual is a control

For cases: $$P_1 = \frac{\exp (Bo + B_1X_1 \ldots + B_{k-1}X_{k-1})}{1 + \exp (Bo + B_1X_1 \ldots + B_{k-1}X_{k-1})} \quad (3)$$

$$Q_1 = \frac{1}{1 + \exp (Bo + B_1X_1 \ldots + B_{k-1}X_{k-1})} \quad (4)$$

For controls: $$P_2 = \frac{\exp (Bo + \ldots + B_{k-1}X_{k-1})}{1 + \exp (Bo + \ldots B_{k-1}X_{k-1})} \quad (5)$$

$$Q_2 = \frac{1}{1 + \exp (Bo \ldots . + B_{k-1}X_{k-1})} \quad (6)$$

By definition, the odds ratio $= \frac{P_1}{Q_2} \div \frac{P_2}{Q_2} = \frac{P_1Q_2}{P_2Q_1}$

By combining equations (3) - (6),

The odds ratio can be expressed as follows:

$$\frac{P_1Q_2}{P_2Q_1} = \frac{\exp (Bo + B_1X_1 + \ldots B_{k-1}X_{k-1})}{\exp (Bo + \ldots B_{k-1}X_{k-1})} \quad (7)$$

$$\ln \frac{P_1Q_2}{P_2Q_1} = (Bo + B_1X_1 + \ldots B_{k-1}X_{k-1}) - (Bo + \ldots B_{k-1}X_{k-1}) \quad (8)$$

$$\ln \frac{P_1Q_2}{P_2Q_1} = B_1$$

Recently, Breslow and Powers, and Prentice and Pyke, have shown that the odds ratio estimates for a case-control study may be obtained by applying the logistic regression model as if the data had been obtained prospectively. Thus, the dependent variable becomes case-control status and the regressor coefficients become estimates of the odds ratio for each risk factor variable.

The purpose of this analyses is to permit adjustment for possible confounding variables without the problem in stratified analyses of empty cells.

The program used to calculate the odds ratios estimates the regression coefficient through an iterative weighted least squares algorithm.

E. Treatment of Variables

The major factors under investigation for their relationship with CHD are the following:

1. Exposure to extrogen/progesterone in the first trimester
2. Exposure to anti-nauseant medication in the first trimester (especially phenothiazines)
3. Exposure to tranquilizers in the first trimester (especially phenothiazines)
4. Occupational exposures of the parents to lead and anesthetic gases prior to and during the first trimester of pregnancy

Data on other possible confounding variables were collected. Selection of confounding variables was made on the basis of association with case/control status and with one of the major factors. Thus, the same variable may have been considered a "confounder" in some instances or an independent variables in others.

1. Dichotomization of Variables

Because of sample size considerations and rarity of exposure to most of the major factors, only two categories could be used for

many variables. Ideally, the choice of the value at which continuous variables or categorical variables are dichotomized should be based on data as to when biologically significant effects occur. For example, the risk of Down's syndrome begins to increase logarithmically after maternal age 30, so dichotomization of maternal age at <30 and 31+ has a biologic basis.

However, for some variables, there was no biologic basis known for established a "cutting point". For many of these variables, dichotomization was based on any exposure during the first three months of pregnancy versus a combination of no exposure and exposure at other times during pregnancy. The rationale for this "cutting point" is based on the premise that cardiac teratogens must act during cardiac development, which is during the first trimester. This premise assumes that exposure prior to or after this time would have no effect. Where possible, data on these variables were examined prior to dichotomization for a peak in risk of exposure during the first trimester.

2. Classification of Occupations and Exposures

Data on the occupation of the parents and other adults residing with the mother were coded according to classifications developed by the United States Department of Commerce, Bureau of Census in the Alphabetic Index of Industries and Occupations. Subsequent groupings were based on similarities of work performed and possible exposures rather than the professional or technical qualifications of the job. For example, nursing aides and orderlies were grouped with registered nurses and physicians under "Health related occupations". An individual was

classified three times, according to the occupation held at the beginning of each of the following time periods: 6 months pre-pregnancy, first 3 months of pregnancy, and last 6 months of pregnancy. If two jobs were held in the same time period, the one with the most number of hours per week was coded.

Possible exposure to lead, janitorial cleansers, and anesthesia was based on a review of the literature documenting such exposure in specific occupations. A list was complied of such occupations, and each job in the three study groups coded according to whether to not it appeared on the list.

Overall lead exposure is a summary variable consisting of reported working with paint with lead, and/or car repair work, and/or smelting with lead, and/or holding a job where lead exposure was possible, based on a literature review as discussed above.

3. Classification by Severity of Lesion

There is current discussion on whether the disparity of finding for risk of CHD with sex hormones may be the result of hormone exposure associated only with severe cardiac lesions. If this is true, there is no a priori reason to believe such an association is limited to the sex hormones only, and to no other potential teratogens. The range of severity of conotruncal lesions in this study made possible the sub-division of cases by the severity of their lesions in order to examine the association with the major exposure variables.

RESULTS

I. INTRODUCTION

This section is divided into four parts corresponding to the four major areas of suspected risk for CHD explored in this study. The first part presents the analyses of risk pertaining to health of the mother prior to and during pregnancy. The second part describes characteristics of the mother and child at birth. In the third part, risks associated with drug use are described. The last part presents analyses of occupations and other environmental exposures, and includes the multiple regression analyses.

Each section contains the frequency distribution for the exposure variables, and comparisons using analyses for strata effects where indicated. The problem of recall bias is briefly addressed in each section.

The variables frequently referred to in this chapter are listed for reference below.

II. MAJOR STUDY VARIABLES

1. Female Sex Hormone Exposure During Pregnancy: Exposure was positive if the subject reported any of the following: a) use of birth control pills while pregnant, b) hormone pills or shots for testing pregnancy and c) hormonal therapy for bleeding during pregnancy.

2. Exposure to Anti-Nauseants in the First Trimester: Exposure was positive if the subject reported any use of anti-nausea

medication during the first trimeaster. Exposure was negative if the subject reported no use after the first trimester.

3. Exposure to Tranquilizers in the First Trimester: Exposure was positive if either of two conditions was met: a) the subject reported tranquilizer use during the first trimester or b) the subject reported use prior to pregnancy and until she found out she was pregnant. In the latter instance, the subject may have indicated no tranquilizer use in pregnancy, but in fact, tranquilizers were used in early pregnancy until the pregnancy was confirmed.

4. Overall Maternal Lead Exposure: This summary variable was positive if the mother reported any one of the following: a) working during the first trimester at a job with possible lead exposure, determined, as discussed in the previous chapter, by comparison with a list of jobs previously shown to have lead exposure. b) Working with paint that contains lead. c) Performing car repair work. d) Working in an area where lead scrap was smelting.

5. Overall Paternal Lead Exposure: Same as for maternal lead exposure.

6. Maternal Alcohol Use: In a similar fashion to exposure to tranquilizers, exposure to alcohol was positive if either of two conditions was met: a) the subject reported alcohol use during the first trimester, or b) the subject reported use prior to pregnancy and until the pregnancy was confirmed. Alcohol equivalents are used to equilibrate the differing amounts of alcohol in various beverages (e.g., wine, beer, etc.)

7. Maternal Smoking: Same as for tranquilizer and alcohol use.

III. HEALTH OF THE MOTHER PRIOR TO AND DURING PREGNANCY

Frequency distributions of the variables pertaining to health before and during pregnancy were examined for difference in the three study populations. Almost all the variables showed no difference among any of the study groups. Table 4.1 presents the variables for which differences were seen.

One variable which was reported significantly more often among cases and Down's syndrome controls was the presence of phlebitis, diagnosed prior to pregnancy. The data for reported phlebitis, regardless of time of diagnoses, showed essentially no difference among the study groups. The fact that mothers of cases and mothers of Down's syndrome controls reported phlebitis prior to pregnancy more frequently than mothers of normal controls may reflect true differences between cases and controls, apparent differences because adjustment for confounding variables is needed, or recall bias. The association may be confounded by older maternal ages, as phlebitis increases with maternal age. Frequency distributions for maternal age groups showing reported phlebitis is displayed in Table 4.2. The difference between cases and random sample controls is not significant in either group, and the frequency among the Down's controls is also not significantly different from the frequency among the other control group. Thus, maternal age appears to explain the excess reporting of phlebitis among mothers of cases and Down's controls.

More mothers of cases than mothers in either control group reported no use of birth control in the year prior to the study pregnancy. Since all three groups reported the same frequency of difficulty in becoming pregnant, this finding probably does not reflect a problem with fertility. It is possible that no birth control was being used because the woman was pregnant, but this study has no data on spacing of pregnancies. The significance of the finding is unclear.

The last variable which was reported significantly more frequently among cases was nausea and vomiting during the entire nine months of pregnancy. (Table 4.1) Although all three study groups reported the same frequency of nausea and vomiting, cases and Down's syndrome controls reported longer duration. When categorized by maternal age, only the young mothers of Down's controls showed a significant difference in duration of nausea from random sample controls. (Table 4.3) The difference between mothers of cases and random sample controls in the older age group is large, but not significant because of small numbers.

If long duration of nausea and vomiting is re-defined as 6 to 9 months duration, then the difference in the older age group between mothers of cases and random sample controls becomes significant. (Table 4.4) However, no differences are observed between mothers of the two control groups, regardless of maternal age.

If the data from both categorization schemes are considered, there appears to be an increased risk associated with long duration of

nausea and vomiting among older mothers of cases. While the data from Table 4.3 suggest this result may reflect bias of recall because mothers of Down's controls also report long duration, it is not clear why a bias should show different age specificities. Data in Table 4.4 suggest the association is not the result of recall bias. A further discussion of the possible biologic significance of this risk is presented in the next chapter.

In summary, most variables on health during pregnancy showed no differences among the study groups. Specifically, the frequencies of reported bleeding during pregnancy, any nausea and vomiting in pregnancy, and accidents were similar in each group. Reported phlebitis in each group, when maternal age was considered, was not different among the study groups. For items pertaining to health before and during pregnancy, there was no evidence of recall bias, and all three study groups reported similar frequencies of events.

The variables reported more frequently by mothers of cases than mothers of controls were long duration (6 to 9 months) of nausea and vomiting in pregnancy, and no use of birth control prior to pregnancy.

IV. CHARACTERISTICS OF MOTHER AND CHILD AT BIRTH

Table 4.5 displays the frequency distribution of some maternal and child characteristics noted at birth.

Associations of variables previously reported to be associated with an increased risk of CHD and Down's Syndrome were also seen in this study. The proportion of babies with low birthweight (i.e., <2500 gm)

was greater among cases, and greater among Down's syndrome controls, compared to random sample controls. About one quarter of CHD cases weighed less than 2500 grams compared to only 6% of random sample controls.

The association of increased maternal age with Down's syndrome was also found; 43% of Down's mothers were over age 30, compared to 12% of random sample controls and 16% of case mothers. Lastly, the association of CHD with multiple births was also found; 5% of CHD cases were multiple births compared to about 2% of normal controls and Down's syndrome controls. The three way cross tabulation of maternal age, parity and case-control status showed no differences.

These data show no differences between cases and controls in terms of the child's race or sex, or maternal parity adjusted for maternal age. The differences noted in birthweight, maternal age, and multiple birth have been reported previously by others.

V. DRUG USE PRIOR TO AND DURING PREGNANCY

Table 4.6 displays frequency distributions for reported drug use prior to and during pregnancy. There was no evidence of excess female hormone use among mothers of cases during pregnancy. No significant differences existed with inadvertent birth control pill use, hormonal pregnancy tests, or hormone injection during pregnancy.

No differenced existed with use of anti-nausea medication during the first trimester. (Table 4.6) About 19% of mothers of cases reported taking medication during this time compared to 17% of mothers

of Down's syndrome and 25% of mothers of controls. Most women in the study groups who used medication took Bendectin(R). There was no evidence that medication use increased with duration of nausea and vomiting for mothers over age 30 in any of the study groups. There was no significant difference among study groups in the proportion who took phenothiazines for nausea in the first trimester, although the numbers are small.

Tranquilizer use, based on reported months of use prior to and during pregnancy, was similar among the three study groups. (Table 4.6) Another category, "use around conception" was developed as described in Chapter 3. This categorization resulted in more mothers of Down's syndrome children reporting exposure to tranquilizers around conception. However, there were still no significant differences between the study groups. Only two mothers reported any phenothiazine use, one in each of the control groups. The most frequent tranquilizers used were the diazepams, Librium (R) and Valium (R).

Table 4.6 shows frequency distributions for cigarette smoking, before and during pregnancy. No differences were noted in the proportions smoking around conception or during the first three months of pregnancy. However, among smoking mothers, significantly more mothers of cases reported smoking greater than 1½ packs per day, compared to mothers in the two control groups.

The preliminary positive findings of heavier smokers and more low-birthweight infants among case mothers compared to the other two control groups suggest that some of the low birthweight among CHD

cases may be attributable to smoking. An adjustment for smoking shows that although the proportion of low birthweight babies may increase slightly among cases as the amount smoked increases, within each smoking category, the proportion of low birthweight cases and Down's controls is greater than the proportion among the random sample controls. (Table 4.7)

The proportion of alcohol users around conception and during the first three months of pregnancy was similar in the three study groups. (Table 4.6) The mean alcohol equivalents consumed per week was greater, although not significantly so among case mothers reporting drinking than mothers of either controls.

In summary, no differences were seen in use of female hormones while pregnant, use of anti-nausea agents, or use of tranquilizers. The small numbers reporting use of phenothiazines do not permit evaluation of risk with this drug group. While similar proportions of women in the three study groups reported cigarette use during pregnancy, the mothers of cases reported heavier use.

A. Drug Use By Severity of Lesion

Table 4.8 to 4.10 show the results of tabulations by severity of lesion as described in Chapter 3. No excess of exposures to female sex hormones, tranquilizers, or anti-nauseants is seen, regardless of categorization scheme, among severe cases. The apparent excess of tranquilizer exposure seen among dead cases is not statistically significant, and is the result of the small number of cases in that category; no difference is observed between random sample controls and cases with severity recategorized according to surgical or autopsy diagnosis. (Table 4.9)

B. Drug Use: Stratified Analysis

A maximum likelihood analysis which estimates odds ratios for risk factors is presented. The cases and random sample controls are allocated to "hospital of birth-birth year" strata, and the procedure assumes a logistic model for strata effects and the common odds ratios.

As Table 4.11 shows, the lack of risk observed in the crude frequencies is also observed for female hormone exposure, anti-nauseant exposure, and tranquilizer exposure. Smoking more than 21 cigarettes per days shows borderline significance; the two significance tests are close to $p = .05$ for an odds ratio of 2.1.

Comparison of the pooled odds ratios and the two summary odds ratios in Table 4.11 reveal very little difference, suggesting the effects of strata are small. Stratified analyses of each variable by year of birth only, and hospital of birth only, did not change the estimates of the odds ratios obtained when the complete strata were modeled.

C. Drug Use: Matched Analysis

A maximum likelihood analysis in which controls are matched to cases by year of birth and hospital of birth is presented. The purpose of performing a matched analysis is to determine if any precision is gained over the stratified analyses. The rationale for conducting a matched analyses, as discussed previously, is based on the fact that several strata contain only one case and its corresponding control; thus, the controls are "matched" by stratification factors to the cases within these strata.

As Table 4.12 shows, the lack of risk oberserved for the drug exposure variable with the stratified analyses persisted with the matched analyses. The estimated odds ratios are not different. Only smoking more than 21 cigarettes per day was consistently associated with case status in both analyses; the estimated odds ratio by either method is about 2.1.

D. Summary: Drug Use

There was no evidence that exposure to female sex hormones in pregnancy, use of anti-nauseants in the first trimester, or tranquilizer exposure in the first trimester was associated with risk of CHD in the offspring. The small numbers of women reporting use of phenothiazines in pregnancy did not permit an evaluation of risk for this drug group. Evaluation of risk by severity of lesion also showed no excess drug exposures.

Smoking more than 21 cigarettes per day was associated with a small risk for CHD.

VI. OCCUPATIONAL EXPOSURES

Data on occupations before and during pregnancy for parents in each study group are presented in Table 4.13. Among mothers, 43% to 47% were working during the first three months of pregnancy. Generally, 84% to 88% of parents were living together during the first 3 months of pregnancy, so maternal exposure to any particulates carried home on the father's work clothes was possible for the majority of mothers. From

2% to 6% of fathers were not working during the mother's first three months of pregnancy. (Table 4.13) The distribution of maternal occupations did not differ between the cases and the two control groups, although there was a suggestion that during the first three months of pregnancy more mothers of cases worked in factory jobs compared to mothers of random controls.

Significantly more fathers of cases were carpenters, compared to fathers of controls. (Table 4.13) More fathers of cases worked in factory jobs than did fathers of controls during each time period, but the difference is significant only in the last 6 months of pregnancy.

More fathers of normal controls were in jobs labeled "protective services" (i.e., armed forces, policeman and firemen), but the difference is significant only for the period six months pre-pregnancy.

An equal percentage in each study group have at least one other working adult residing with the mother 6 months prior to and/or during pregnancy. (Table 4.13) The numbers are small within each study group so that differences in occupation and job location are not significant.

Frequency distribution of possible exposure to lead are tabulated for parents of cases and both sets of controls. (Table 4.14) Among mothers, only 1 mother of a case and 2 mothers of random sample controls had jobs with possible lead exposure, so the data are not tabulated. Among fathers, possible occupational exposure to lead tended to be more frequent for fathers of cases than fathers of controls, but the differences are not significant. Fathers and to a lesser extent, mothers of cases also reported more exposure to paint containing lead,

and to smeltering or soldering with lead. In contrast, there were no differences in parental reporting of exposure to domestic or janitorial cleansers or to anesthesia. (Table 4.14)

Only five industries had enough employees to warrant display of data. Of these five, more fathers of cases worked for Company D then did fathers in either control group. Equal numbers in each group worked for the other four companies. Company D produces telephone cables, cords and apparatus, and the employees are mostly factory workers. The risk associated with working for this company independent of the risk of exposures noted above will be assessed in the following sections.

A. Summary

In general, the data are suggestive of increased frequency of various exposures to lead among case parents. In addition, paternal employment as a carpenter, in a factory, or employment by Company D were also reported more frequently among families of cases. No increase in parental exposure to anesthesia among parents of cases was seen.

B. Occupation and Exposure by Severity of Lesion

The occupations and exposures suggested to be risk factors in the previous section were examined for possible association with cases classified according to severity of lesion. For this and subsequent analyses, two variables on overall parental lead exposure were developed as discussed previously. Briefly, the variables represent a combination of possible job exposure to lead, based on literature review, and reported exposure to lead via soldering or painting.

The increased frequency of maternal exposure among severely affected cases is significant. (Table 4.15) While there was no difference among the study group if all CHD is grouped, there was a significant difference in exposure between the more severe CHD and either control group. The frequency of exposure among the mothers of Down's syndrome children was very low; sub-classification by severity of lesion showed no differences.

Likewise, the increased frequency of paternal lead exposure among severely affected cases is statistically significant. (Table 4.16) Exposure frequency among the Down's syndrome controls showed no differences by severity.

Frequency of paternal exposure to lead-based paint, and work as a carpenter were both higher in severely affected cases, regardless of the method of categorizing severity. (Table 4.17, 4.18) The actual numbers of men employed as carpenters was very small, however, making the frequencies in each severity group is somewhat unstable (e.g., only one father of a Down's child is a carpenter).

Categorization by severity of lesion did not show consistent difference in exposure frequencies for fathers employed by Company D (Table 4.19) or fathers employed as factory workers. (Table 4.18)

In summary, the most striking differences are the increased frequency of both maternal and paternal overall lead exposure variables among severely affected cases compared to frequencies in either control group.

These results are unlikely to be the result of recall bias among parents of cases, for two reasons. One, bias would occur only

if control parents forgot their own or their spouses occupations and/or case parents recalled occupations different from the ones they actually had in terms of the exposures of interest.

Two, the parents of the Down's Syndrome controls responded similarly to the other controls on questions of reported exposures. This was true for drug exposures and occupational exposures. Therefore, in subsequent analyses, the Down's syndrome controls are not used.

C. Occupation and Exposures: Stratified Analysis

The estimated odds ratios for occupational exposures obtained by analyses which consider strata effects, are shown in Table 4.20. The odds ratios for overall maternal and paternal lead exposure, and paternal exposure to lead smelting are not significant. Paternal exposure to paint with lead, employment as a carpenter, and employment by Company D are significantly associated with a risk of CHD in the offspring (odds ratios 2.2, 4.7, and 5.1 respectively). Paternal employment in a factory shows borderline significance, with the two significance tests close to $p = .05$ for odds ratios of 1.97.

The comparison of the pooled odds ratios and the two summary odds ratios in Table 4.20 show very little difference, suggesting the effects of strata are small. Stratified analyses of each variable by year of birth only, and hospital of birth only, do not change the estimates of the odds ratios obtained when the complete strata are modelled, with one exception: the variable of paternal employment in a factory. For this variable, the effects of hospital of birth appear to be important. The odds ratio for the risk of CHD with paternal

employment in a factory is significant when hospital of birth is considered, but not if strata are year of birth only or strata effects are ignored. (Table 4.21)

Stratified analysis is done for variables previously shown to be associated with severity of the lesion. In order to compare the separate odds ratios between the two groups of cases (i.e. more severe and less severe), controls were assigned to each case as they would be for the matched analysis; therefore, the odds ratios are independent. The measure of severity of lesion used in this analysis is whether or not the case had surgery and/or autopsy performed. As noted with the frequency distributions, either measure gave essentially similar findings. Table 4.22 shows the results for overall parental lead exposure. The increased frequency of paternal overall lead exposure among severely affected cases compared to controls is not significant when the effects of strata are considered. However, maternal overall lead exposure is significantly associated with case status among the severe cases.

Categorization by severity of lesion for paternal occupations and exposure are shown on Table 4.23. Sub-categorization by severity of lesion results in only 5 men working as carpenters within each category, so while the estimated odds ratios are greater than unity for each severity category, they are significant only for cases with severe lesion. Paternal jobs in a factory and paternal exposure to paint with lead show no difference by severity of lesion.

1. Summary

A stratified analysis which estimated odds ratios for risk factors is presented. Significant findings included increased risk with paternal employment as a carpenter, in a factory, employment by Company D and exposure to paint with lead. The effects of strata appear to be small.

Sub-categorization by severity of lesion showed that maternal lead exposure is significantly associated with severe lesions. Also, the odds ratio for paternal employment as a carpenter is much greater for cases with severe lesions compared to less severe lesions, although small numbers render the ratios very unstable.

D. Occupation and Exposure: Matched Analyses

Table 4.24 shows the comparison of estimated odds ratios derived from both stratified and matched analyses for parental occupations and exposures. The estimates derived from the two analyses are not different, and show significant association of case status with paternal employment as a carpenter, in a factory, in Company D, and paternal exposure to paint with lead.

There is no evidence of improved precision with matched analyses compared to stratified analyses. In fact, for some comparisons the confidence interval was wider with matched analyses because sets with the case or all controls having missing data on a variable were not included. Therefore, no further analyses in which the controls are considered matched to cases were done.

E. Occupation and Exposure: Explanatory Variables

The preliminary positive findings with parental employment and exposures may result from some degree of overlap among the variables. Therefore, the following tables are presented to assess the extent to which certain exposure varaibles may explain the risk associated with other variables.

As shown in Tables 4.25 and 4.26, the risk of CHD associated with paternal employment as a carpenter is not significant when maternal smoking and exposure to paint with lead are held constant. These two variables, may be explaining the apparent risk associated with employment as a carpenter.

Tables 4.27 to 4.29 show that the risk with paternal employment in a factory is not explained by paint exposure or maternal smoking, but the risk is reduced when controlled for employment by Company D. Each odds ratio in these three tables was evaluated over hospital strata as well, since prior analysis showed the significance of strata effects. Although few families were employed by Company D, proportionately more factory workers among cases were employed than among controls, so the overall odds ratio for paternal employment in a factory was reduced and became nonsignificant. Nevertheless, whatever the specific exposures of the factory workers may be, it should be evaluated for all employees, not just one company, since it is the combined risk that is significant.

The risk associated with exposure to paint with lead is not changed when adjusted for maternal smoking. (Table 4.30) However, the odds ratios are heterogeneous between the smoking categories; the risk is less than one for CHD among heavy smokers whose husbands were exposed

to paint. The confidence interval around 0.188, the proportion of heavy smoking mothers of cases whose husbands were exposed to paint, includes 0.318, the comparable proportion among mothers of controls. Thus, the apparent interaction of heavy smoking and paint exposure is most likely the result of small numbers of exposed in both study groups.

F. Summary

As these tabulations show, the variables which appear to be associated with a risk of CHD independent of association with other variables are the following: maternal smoking, paternal exposure to paint with lead, paternal employment by Company D, and possibly paternal employment in a factory.

Simultaneous adjustment for possible confounding among several variables is better achieved using a multiple regression model, presented in the next section.

G. Multiple Logistic Regression

The multiple logistic regression analysis was used to control for any confounding among the major exposure variables. Traditionally, for a case-control study, the dependent variable is an exposure variable, and case/control status and other covariables are entered as the "independent" variable. This retrospective model does not permit an obvious interpretation of interactions between case-control status and other covariables.

However, as discussed previously, recent publications have argued that the prospective and retrospective models give equivalent

estimates provided the model is saturated in the covariables. An example of this equivalency is shown in Table 4.31, where a simple model of the effects of paint exposure and cigarette smoking is examined. The estimated odds ratios for paint exposure by the two models are the same, as are the regression coefficient for the interaction term. The similarity of the odds ratio estimates if the prospective model is not fully saturated depends on the significance of the product terms.

For the logistic regression analysis in this study, the odds ratios were derived using the prospective model with interaction terms between paint exposure and cigarette use, and between nausea for 6 to 9 months and maternal age. These were the only potentially important interactions discovered in prior analyses. The odds ratios derived in this fashion were checked against odds ratios derived from the classic retrospective model, and differences reported.

The variables which had odds ratios significantly different than 1 were the following: smoking more than 21 cigarettes per day, paternal job as a carpenter, nausea and vomiting in pregnancy among older case mothers, and low birthweight. (Table 4.32) Each variable will be discussed more fully below.

Smoking more than 21 cigarettes per day was significantly associated with risk of CHD when evaluated using the prospective model; the adjusted odds ratio is 2.88. The odds ratio derived from the retrospective model, (i.e., where smoking is the dependent variable) was not significant; the value was 1.74. Both values are within the confidence interval proscribed by the prospective model. The difference in values

is due to the differences in the model: in the retrospective model the variable on paternal employment by Company D had to be deleted so the values for the coefficients would converge; in the prospective model, smoking and paint exposure were combined to test for interaction, so the variable "smoking >20 cigarettes per day" excludes anyone with paint exposure. Although the adjusted odds ratio of 0.52 for interaction of paint and smoking >20 cigarettes per day is not significant, it may have been sufficient to reduce the smoking odds ratio in the retrospective model. In summary, the results of the multiple adjustment regression analyses suggest maternal smoking >20 cigarettes/day is a risk factor for CHD, independent of its association with other risk factors.

Paternal employment as a carpenter is significantly associated with a risk of CHD, regardless of the model used. The adjusted odds ration is 5.60 for the prospective model, and 6.09 for the retrospective model. The higher rate in the retrospective model is due to the deletion of the variable on paternal paint exposure in order to allow convergence in the estimation procedure. Exposure to paint and employment as a carpenter are highly associated, and prior analyses suggested that paint exposure explained the risk of employment as a carpenter. However, multiple regression analyses adjusted for other variables associated with paint exposure, such as maternal smoking, employment in a factory, etc. and the risk for employment as a carpenter emerged.

Although neither long duration of nausea and vomiting alone nor maternal age over 30 alone were significantly associated with a risk of CHD, the interaction of these 2 variables was an important risk. (It

was not estimated from a retrospective model.) The wide confidence interval, 1.8 to 54.6, reflects the scarcity of individuals who actually were in that category.

The risk of CHD associated with low birthweight has been a consistent finding. Whether it should be thought of as an outcome measure, like CHD, rather than a risk factor is discussed in the next chapter.

Paternal exposure to paint with lead, when evaluated using the prospective model was not quite significant; the adjusted odds ratio was 2.00. The odds ratio derived from the retrospective model, 2.44, was significant, but the variable on carpenter employment had to be deleted, otherwise the regression estimates could not converge. A reasonable interpretation of these conflicting data could be that paternal paint exposure appears to be a risk factor for CHD, because in the prior 3 way tabulation analyses, the risk was constant across maternal smoking, across employment as a carpenter, or in a factory. The retrospective multiple logistic regression model also confirmed these findings, although one risk factor, carpenter employment, could not be entered in the model. However, in the prospective model, all of these other variables were held constant and the odds ratio, still greater than one, was no longer significant. Perhaps with greater numbers of cases and controls, the significance of the risk would be greater.

Paternal employment in a factory was not associated with a risk of CHD by either multiple logistic regression model. Even when hospital of birth strata were modelled, the risk was not significant. It appears that other confounding variables have explained the risk of factory employment.

Paternal employment by Company D was not significantly associated with a risk of CHD using the prospective model. Constructing a retrospective model comparable in number of variables to the prospective model was not possible as the maximum likelihood estimates never converged; there were no positive values for several variables among the few men who worked for Company D. The wide confidence interval, 0.57 to 16.25, is further evidence of the few numbers of subjects in this category.

1. Summary: Multiple Logistic Regression

Variables significantly associated with risk of CHD were shown to be paternal employment as a carpenter; interaction of maternal age and nausea for 6+ months, and low birthweight. Maternal smoking, more than 21 cigarettes per day and paternal exposure to paint with lead showed equivocal results, depending on the model employed, but in both cases the odds ratios were greater than one.

2. Multiple Logistic Regression for Severe Cases

Prior analysis had shown several variables to be associated with severe cases only. In particular, the overall parental lead exposure variables were significantly associated with risk of CHD. The categorization of severity was based on surgical or autopsy confirmation of lesion, as discussed in the methods section. The controls were matched to cases as per the matched analyses, and only those controls matched to severe cases were used. Therefore, for this analysis, only 61 cases with severe lesions and 175 controls were used.

Only those variables previously suspected to be associated with severe CHD were entered into the model. In addition, only estimates from the retrospective model are presented, since estimates from the prospective model were sufficiently dissimilar to suggest inequality. As Table 4.33 shows, the odds ratio for overall maternal lead exposure is not significant, when controlled for cigarette smoking, paternal paint and lead exposure, and paternal employment in a factory or as a carpenter. The odds ratio was 3.13, with 95% confidence interval from 0.79 to 12.42. The odds ratio is not dissimilar to that calculated with the stratified analyses, but the inclusion of the five covariables decreased the level of significance. Overall paternal lead exposure showed similar findings, with the adjusted odds ratio of 1.75 not quite significant.

Paternal employment as a carpenter and paternal exposure to paint both showed odds ratios greater than one, but were not significant when adjusted for the other covariables.

A major problem encountered with performing a multiple regression analyses on exposure variables where the absolute probability of exposure is very low is that more observations are required to reach a level of significance than was possible with this study. Thus, while the odds ratios are consistent with previous findings, small numbers have reduced the significance level.

VII. SUMMARY

Data analyses for this study consisted of using frequency distributions, stratified analyses, matched analyses, and multiple

adjustment with a logistic regression model in order to identify possible risk factors among several groups of variables.

Among the group of variables on maternal health prior to and during pregnancy, a risk of CHD was associated with nausea and vomiting longer than 6 months during pregnancy among women over age 30. Also, a deficit was seen of mothers of cases using any contraceptive method in the year prior to the study pregnancy.

An excess of multiple births and low birthweight babies were observed among the cases compared to the controls; both observations have been made previously by other investigators.

There appeared to be no risk associated with using female sex hormones or tranquilizers (primarily Librium^{R} and Valium^{R}) in the first trimester. Despite the finding of increased risk with long duration of nausea and vomiting, there was no increased risk associated with use of anti-nauseants (primarily Bendectin^{R}). Too few phenothiazines were taken to permit an evaluation of risk with this group of drugs.

Maternal smoking more than 21 cigarettes per day was associated with a small but significant increased risk of CHD.

Among the occupational and environmental exposure variables, an excess risk of CHD was observed with paternal employment as a carpenter. The risk associated with paternal employment with Company D did not remain significant after multiple adjustment for other variables. However, small numbers of employees resulted in a wide confidence interval on the adjusted odds ratio. More data would be needed to be certain of significant risk.

The variables on overall parental lead exposure were associated with an increase risk of severe CHD in the stratified and matched analyses. The risk was not significant in the multiple logistic regression analyses, but small numbers in this analysis made the interpretation of significance levels of the risk estimates difficult. The odds ratios are consistently greater than one and suggestive of risk with parental lead exposure. In particular, most of the analyses were suggestive of an increased risk associated with paternal exposure to paint with lead.

VIII. CONCLUSION

This study of risk factors for conotruncal malformations has attempted to explore possible associations of drug use in pregnancy and parental occupation and occupational exposures. The most helpful leads for new risk factors are possible occupation exposures. Notably, the risk of conotruncal malformations has been observed with paternal exposure to paint, employment as a carpenter, and employment by a specific company in Baltimore. Although these findings are preliminary they do suggest that not only maternal but paternal occupational and environmental exposures may be important in the etiology of CHD, and birth defects in general.

TABLE 4.1

Frequency Distribution of Variables on Health Prior to and During Pregnancy Among Cases, Random Sample Controls, and Down's Syndrome Controls

Variable	Cases %	Cases Totals	Random Sample Controls %	Random Sample Controls Totals	Down's Syndrome Controls %	Down's Syndrome Controls Totals
Phlebitis		(116)		(330)		(120)
Diagnosed prior to pregnancy	5.2%		1.5%		4.2%	
Diagnosed during pregnancy	0.9%		2.1%		0%	
Diagnosed after pregnancy	1.7%		2.4%		1.7%	
Type of Birth Control Measures Used Year Before Pregnancy		(117)		(334)		(120)
None	60.0%		42.8%		42.5%	
Birth control pill (± other forms)	25.6%		35.0%		25.0%	
Diaphragm (± other forms)	3.4%		3.0%		9.2%	
IUD (± other forms)	1.7%		4.5%		5.8%	
Condom (± other forms)	11.1%		13.2%		10.8%	
Nausea and Vomiting						
Anytime During Pregnancy	69.0%	(116)	70.9%	(333)	67.2%	(119)
Nine months of nausea and vomiting	8.7%	(115)	3.6%	(333)	7.7%	(117)

TABLE 4.2

Phlebitis Within Maternal Age Groups for Cases, Random Sample Controls, and Down's Syndrome Controls

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Age <30	Reported Phlebitis	4	4	2
	No Phlebitis	93	288	66

(1) Difference between cases and random sample controls N.S. Z = 1.576 p >.05
(2) Difference between Down's Syndrome controls and random sample controls N.S. Z = 0.899 p >.05

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Age 30+	Reported Phlebitis	2	1	3
	No Phlebitis	17	37	49

(1) Difference between cases and random sample controls N.S. Z = 1.168 p >.05
(2) Difference between Down's Syndrome controls and random sample controls N.S. Z = 0.696 p >.05

$$Z = \frac{\ln (\text{odds ratio})}{\sqrt{\Sigma \frac{1}{\text{cell frequency}}}} \qquad \text{(see text)}$$

TABLE 4.3

Nine Months of Nausea Within
Maternal Age Groups for Cases, Random Sample Controls,
and Down's Syndrome Controls

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Age <30	Nausea for 9 months	6	10	7
	Nausea 0-8 months	91	284	60

(1) Difference between cases and random sample controls: $Z = 1.8$ $p > .05$
(2) Difference between Down's Syndrome controls and random sample controls: $Z = 2.34$ $p < .05$

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Age 30+	Nausea for 9 months	4	2	2
	Nausea 0-8 months	14	37	48

(1) Difference between cases and random sample controls: $Z = 1.80$ $p > .05$
(2) Difference between Down's Syndrome controls and random sample controls: $Z = 0.25$ $p > .05$

$$Z = \frac{\ln (\text{odds ratio})}{\sqrt{\Sigma \frac{1}{\text{cell frequency}}}}$$

TABLE 4.4

Six to Nine Months of Nausea Within
Maternal Age Groups for Cases, Random Samples Controls and
Down's Syndrome Controls

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Age <30	6-9 Months nausea	10	29	9
	0-5 Months nausea	87	265	58

(1) Different between cases and random sample controls: $z = .127$ $p > .05$
(2) Difference between Down's Syndrome controls and sample controls:
$Z = 0.856$ $p > .05$

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Age 30+	6-9 Months nausea	8	3	4
	0-5 Months nausea	10	36	46

(1) Difference between cases and random sample controls: $Z = 2.95$ $p < .05$
(2) Difference between Down's Syndrome controls and random sample controls:
$Z = .053$ $p > .05$

$$Z = \frac{\ln (\text{odds ratio})}{\sqrt{\Sigma \frac{1}{\text{cell frequency}}}}$$

TABLE 4.5

Frequency Distributions of Maternal and Child Characteristics
At Birth Of Cases, Random Sample Controls,
and Down's Syndrome Controls

Variable	Cases % (N=117)	Random Sample Controls % (N=334)	Down's Syndrome Controls % (N=120)
1. Child's race: white	78.6%	75.7%	70.8%
2. Birthweight <2500 gm.	24.9%	5.7%	17.5%
3. Maternal Age at Birth			
≤20	24.8%	24.9%	15.0%
21-25	31.6%	32.6%	22.5%
26-30	27.4%	30.8%	19.2%
31-35	11.1%	7.5%	18.3%
36+	5.1%	4.2%	25.0%
4. Child's sex: male	54.7%	53.0%	53.5%
5. Single birth	94.9%	97.9%	98.3%
Twin 1	1.7%	1.8%	0%
Twin 2	3.4%	0.3%	1.7%
6. Total previous pregnancies:			
0	37.6%	41.6%	29.2%
1	35.9%	29.0%	28.3%
2+	25.6%	29.3%	42.5%

TABLE 4.6

Cross Tabulations of Variables in Maternal Drug Use
by Case-Control Status

Variable	Cases %	Cases Total	Random Sample Control %	Random Sample Control Total	Down's Syndrome Control %	Down's Syndrome Control Total
1. Estrogens/Progestins:						
Birth control pill use prior to pregnancy only	25.0%	(116)	32.0%	(331)	23.3%	(120)
Birth control pill use while pregnant	3.4%	(116)	3.0%	(331)	1.7%	(120)
Hormonal pregnancy test	3.4%	(117)	2.4%	(331)	5.8%	(120)
Hormone injections for pregnancy	5.1%	(117)	4.2%	(334)	3.3%	(120)
2. Antinauseant use:						
In 1st trimester	19.3%	(114)	25.1%	(334)	17.1%	(117)
% using phenothiazines	13.6%	(22)	6.0%	(83)	5.0%	(20)
3. Tranquilizer agent use:		(115)		(332)		(118)
6 mos. pre-pregnancy only	4.3%		2.1%		5.1%	
1st 3 mos. pregnancy	2.6%		5.1%		6.8%	
Use other than above	6.1%		5.1%		3.4%	
Use around conception	3.4%	(116)	5.4%	(333)	10.1%	(119)
% using Librium, Valium	75%	(4)	67%	(18)	50%	(50)
4. Cigarette smoking:		(117)		(334)		(120)
6 mos. pre-pregnancy only	7.5%		3.9%		1.7%	
1st 3 mos. pregnancy	35.9%		41.0%		35.8%	
Use other than above	0.8%		1.8%		0%	
Use around conception	41.4%	(116)	42.8%	(334)	36.7%	(120)
Largest number smoked/day		(117)		(331)		(119)
1-10	15.4%		20.8%		17.6%	
11-20	14.5%		17.8%		13.4%	
21-30	6.0%		4.2%		3.4%	
31+	8.5%		3.3%		3.4%	

TABLE 4.6 (Cont'd.)

Variable	Cases %	Cases Total	Random Sample Controls %	Random Sample Controls Total	Down's Syndrome Controls %	Down's Syndrome Controls Total
5. Alcohol use:						
6 mos. pre-pregnancy only	4.3%	(117)	5.7%	(331)	7.5%	(120)
1st 3 months pregnancy	16.2%		16.3%		24.2%	
Use other than above	6.0%		4.2%		1.7%	
Use around conception	26.5%		25.4%		31.7%	
Alcohol equivalents per week (mean)	(34.2)		(24.7)		(28.2)	
Alcohol equivalent per week among those who reported drinking (mean)	(128.9)		(95.5)		(84.5)	

TABLE 4.7

Low Birthweight by Maternal Smoking Categories for Cases, Random Sample Controls, and Down's Syndrome Controls

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Nonsmokers	Birthweight ≤2.5 kg	13	6	8
	Birthweight >2.5 kg	52	172	64

(1) Difference between cases and random samples controls: $Z = 3.79$ $p < .05$
(2) Difference between Down's Syndrome controls and random sample controls: $Z = 2.22$ $p < .05$

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Smoke 1-20 cigarettes/ day	Birthweight ≤2.5 kg	9	11	11
	Birthweight >2.5 kg	26	117	25

(1) Difference between cases and random sample controls: $Z = 3.44$ $p < .05$
(2) Difference between Down's Syndrome control and random sample cases: $Z = 3.22$ $p < .05$

		Cases[1]	Random Sample Controls	Down's Syndrome[2] Controls
Smoke 21+ cigarettes per day	Birthweight ≤2.5 kg	6	1	3
	Birthweight <2.5 kg	11	24	5

(1) Difference between cases and random sample controls: $Z = 2.26$ $p < .05$
(2) Difference between Down's Syndrome controls and random sample controls: $Z = 2.13$ $p < .05$

TABLE 4.8

Female Sex Hormone Exposure During the First Trimester by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	12.4%	(113)	9.0%	(332)	10.2%	(118)
Less Severe	12.5%	(48)	--		12.3%	(73)
More Severe	12.3%	(65)	--		6.5%	(45)
Alive	13.6%	(88)	--		12.2%	(98)
Dead	8.0%	(25)	--		0%	(20)

TABLE 4.9

Exposure Around Conception to Tranquilizers by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	3.5%	(115)	6.0%	(332)	10.1%	(118)
Less Severe	0%	(48)	--		10.7%	(75)
More Severe	6.0%	(67)	--		9.3%	(43)
Alive	0	(90)	--		11.2%	(98)
Dead	16.0%	(25)	--		5.0%	(20)

TABLE 4.10

First Trimester Exposure to Anti-Nauseant Medication by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	19.3%	(114)	25.1%	(334)	17.1%	(117)
Less Severe	16.3%	(48)	--		19.4%	(72)
More Severe	20.6%	(66)	--		13.3%	(45)
Alive	20.2%	(89)	--		13.5%	(98)
Dead	16.0%	(25)	--		21.0%	(19)

TABLE 4.11

Estimated Odds Ratios for Drug Exposure Variables
Comparing Cases and Random Sample Controls: Stratified Analyses

Factor	Pooled Odds Ratio	Maximum Likelihood Odds Ratio	Lower & Upper 95% Limit	Likelihood Ratio test	P	Mantel Haenszel Summary Odds Ratio	Mantel Haenszel Summary χ^2	P
Female Sex Hormone Exposure	1.42	1.31	0.64-2.68	0.55	p =.45	1.31	0.32	p =.57
Anti-Nauseant Exposure (first trimester)	0.71	0.66	0.39-1.13	2.43	p =.12	0.65	1.97	p =.16
Tranquilizer Exposure (first trimester)	0.52	0.54	0.18 1.63	1.33	p =.25	0.56	0.75	p =.39
Smoking > 21 cigarettes/ day	2.03	2.08	1.03-4.17	4.06	p =.04	2.05	3.59	p =.058

TABLE 4.12

Comparison of Odds Ratios for Drug Exposure Variables Between Stratified Analysis and Matched Analysis

	Stratified Analyses				Matched Analyses			
Factor	Odds Ratio	Lower & Upper 95% Limits	Likelihood Ratio Test	P	Odds Ratio	Lower & Upper 95% Limits	Likelihood Ratio Test	P
Female Sex Hormone Exposure	1.31	0.64 - 2.68	0.55	p >.25	1.37	0.66 - 2.82	0.69	p >.25
Anti-Nauseant Exposure (first trimester)	0.66	0.39 - 1.13	2.43	p >.10	0.65	0.38 - 1.11	2.58	p >.10
Tranquilizer Exposure (first trimester)	0.54	0.18 - 1.63	1.33	p= .25	0.57	0.19 - 1.71	1.11	p >.25
Smoking >21 cigarettes/day	2.08	1.03 - 4.17	4.06	p <.05	2.14	1.04 - 4.38	4.28	p <.05

TABLE 4.13

Cross Tabulations of Variables in Occupations and Exposures by Case-Control Status

Variable	Cases %	Cases Total	Random Sample Controls %	Random Sample Controls Total	Down's Syndrome Controls %	Down's Syndrome Controls Total
A. Mother - 6 mos. pre-pregnancy		(117)		(332)		(120)
Not working	50.4%		53.6%		59.2%	
Work - Health field	8.5%		8.4%		5.0%	
Teacher	2.6%		4.5%		6.7%	
Sales/personal service	9.4%		7.2%		8.3%	
Clerk/secretary	16.2%		11.7%		9.2%	
Factory	6.8%		4.2%		3.3%	
Other	6.1%		10.4%		8.3%	
B. Mother: 1st 3 months of pregnancy						
Not working	53.0%		55.1%		56.7%	
Work - Health field	6.8%		7.8%		5.8%	
Teacher	2.6%		4.8%		5.8%	
Sales/personal service	9.4%		6.9%		7.5%	
Clerk/secretary	14.5%		11.1%		10.0%	
Factory	6.8%		3.6%		5.0%	
Other	6.9%		10.7%		9.2%	
C. Mother: last 6 months of pregnancy						
Not working	59.8%		62.3%		63.3%	
Work - Health field	6.8%		7.5%		5.8%	
Teacher	2.6%		3.9%		3.3%	
Sales/personal service	9.4%		5.7%		5.0%	
Clerk/secretary	12.0%		9.0%		9.2%	
Factory	3.4%		2.7%		5.0%	
Other	6.0%		8.9%		8.4%	
Mother & Father cohabitate in 1st 3 months of pregnancy	84.5%	(116)	83.5%	(333)	87.5%	(120)

TABLE 4.13 (Cont'd.)

Variable	Cases %	Cases Total	Random Sample Controls %	Random Sample Controls Total	Down's Syndrome Controls %	Down's Syndrome Controls Total
D. Father: 6 mos. pre-pregnancy		(112)		(327)		(114)
Not working	1.8%		6.4%		4.3%	
Work - Health field	3.6%		4.3%		1.7%	
Teacher	1.8%		3.7%		4.3%	
Sales/personal service	13.4%		13.8%		18.8%	
Construction	4.5%		5.2%		7.7%	
Machinist/mechanic	9.8%		7.0%		5.1%	
Carpenter	5.4%		1.5%		0.9%	
Factory	16.1%		9.8%		6.0%	
Protective service	1.8%		8.3%		4.3%	
Drivers/gas attendents	5.4		5.8%		9.4%	
Other	36.4%		34.2%		31.5%	
E. Father: 1st 3 months of pregnancy		(112)		(328)		(117)
Not working	1.8%		6.1%		3.4%	
Work - Health field	3.6%		4.0%		1.7%	
Teacher	1.8%		3.7%		4.3%	
Sales/personal service	13.4%		13.7%		18.8%	
Construction	4.5%		5.5%		6.8%	
Machinist/mechanic	9.8%		7.6%		5.1%	
Carpenter	5.4%		1.5%		0.9%	
Factory	17.0%		10.4%		6.0%	
Protective services	2.7%		7.6%		4.3%	
Drivers/gas attendents	5.4%		5.8%		9.4%	
Other	34.6%		34.1%		39.3%	
F. Father: last 6 months of pregnancy		(112)		(328)		(117)
Not working	1.8%		5.2%		4.3%	
Work - Health field	3.6%		4.3%		1.7%	
Teacher	1.8%		3.4%		4.3%	
Sales/personal service	13.4%		14.6%		18.8%	
Construction	5.4%		4.9%		6.8%	
Machinist/mechanic	8.9%		7.9%		5.1%	
Carpenter	5.4%		1.5%		0.9%	
Factory	18.8%		11.3%		6.0%	
Protective services	1.8%		7.4%		4.3%	
Drivers/gas attendents	5.4%		5.2%		9.4%	
Other	33.7%		34.3%		38.4%	

TABLE 4.13 (Cont'd.)

Variable	Cases %	Cases Total	Random Sample Controls %	Random Sample Controls Total	Down's Syndrome Controls %	Down's Syndrome Controls Total
G. Presence of other working adult in house with mother	14.7%	(116)	14.7%	(334)	15.3%	(118)
H. Other adult occupation (during 1st 3 months of pregnancy)		(15)		(38)		(17)
Manager	13.3%		10.5%		5.9%	
Sales/personal service	13.3%		10.5%		11.8%	
Clerk/secretary	6.7%		2.6%		11.8%	
Construction	6.7%		7.9%		11.8%	
Factory	13.3%		23.7%		23.5%	
Non-specific laborer	26.7%		18.4%		23.5%	
I. Other Adult Job Location		(16)		(39)		(15)
Company A	18.8%		10.3%		-	
Other	81.2%		89.7%		100%	

TABLE 4.14

Frequency Distributions of Parental Exposures and Job Location for Cases, Random Sample Controls, and Down's Syndrome Controls

Variable	Cases %	Cases Total	Random Sample Controls %	Random Sample Controls Total	Down's Syndrome Controls %	Down's Syndrome Controls Total
Maternal Exposure to Lead	6.0%	(116)	2.7%	(331)	1.7%	(118)
Mother: worked with paint with lead	3.4%	(116)	1.8%	(332)	1.7%	(118)
Mother: worked with smelter/solder with lead	3.4%	(117)	0.3%	(332)	0%	(119)
Paternal Exposure to Lead	37.6%	(109)	26.6%	(301)	28.3%	(113)
Exposure to lead in Father's job (see text)	21.1%	(114)	13.8%	(326)	10.3%	(117)
Father: worked with paint with lead	18.8%	(108)	9.5%	(305)	6.1%	(115)
Father: worked with smelter/solder with lead	15.2%	(112)	8.9%	(302)	8.8%	(113)
Mother: Exposure to anesthesia (occupation)	0.9%	(117)	1.8%	(330)	0%	(119)
Father: Exposure to anesthesia (occupation)	0.9%	(115)	1.9%	(319)	0%	(115)
Mother: Exposure to domestic/ janitorial cleanser	6.8%	(117)	4.5%	(331)	2.5%	(120)
Father: Exposure to domestic/ janitorial cleanser	7.1%	(112)	13.1%	(312)	8.8%	(114)
Father's Job Location (anytime)						
Company A	3.6%		3.1%		4.3%	
Company B	1.8%		0.9%		1.7%	
Company C	0.9%		2.2%		2.6%	
Company D	4.5%		0.9%		0.9%	
Company E	0.9%		0.6%		1.7%	
Other	87.5%		86.9%		86.2%	

TABLE 4.15

Maternal Lead Exposure by Severity of Lesion and Mortality Status for Cases, Random Sample Controls and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	6.0%	(116)	2.7%	(331)	1.7%	(118)
Less Severe	2.0%	(49)	--		2.7%	(73)
More Severe	9.0%	(67)	--		0%	(45)
Alive	4.4%	(91)	--		2.0%	(98)
Dead	12.0%	(25)	--		0%	(20)

TABLE 4.16

Paternal Lead Exposure by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	37.6%	(109)	26.6%	(301)	22.8%	(113)
Less Severe	31.8%	(44)	--		21.4%	(70)
More Severe	41.5%	(65)	--		20.9%	(43)
Alive	36.5%	(85)	--		23.4%	(94)
Dead	41.7%	(24)	--		10.5%	(19)

TABLE 4.17

Father Exposed to Lead-based Paint by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	18.8%	(108)	9.5%	(305)	6.1%	(115)
Less Severe	15.9%	(44)	--		5.6%	(71)
More Severe	21.9%	(64)	--		6.7%	(44)
Alive	17.9%	(84)	--		7.3%	(96)
Dead	25.0%	(24)	--		0%	(19)

TABLE 4.18

Paternal Occupation by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases				Random Sample Controls				Down's Syndrome Controls			
	Carpenter		Factory Worker		Carpenter		Factory Worker		Carpenter		Factory Worker	
	%	(Total)	%	(Total)	%	(Total)	%	(Total)	%	(Total)	%	(Total)
All Subjects	5.4%	(112)	17.0%	(112)	1.5%	(328)	10.4%	(328)	0.9%	(117)	6.0%	(117)
Less Severe	4.3%	(46)	17.4%	(46)					0%	(74)	8.1%	(74)
More Severe	5.9%	(68)	19.1%	(68)					2.2%	(43)	4.4%	(43)
Alive	2.2%	(89)	16.0%	(25)					0%	(98)	7.1%	(98)
Dead	19.1%	(89)	16.0%	(25)					5.3%	(19)	5.3%	(19)

TABLE 4.19

Father Employed by Company D by Severity of Lesion and Mortality Status for Cases, Random Sample Controls, and Down's Syndrome Controls

	Cases		Random Sample Controls		Down's Syndrome Controls	
	%	(Total)	%	(Total)	%	(Total)
All Subjects	4.5%	(112)	0.9%	(321)	0.9%	(116)
Less Severe	2.3%	(44)	--		1.4%	(73)
More Severe	5.9%	(68)	--		0%	(43)
Alive	4.7%	(87)	--		1.0%	(97)
Dead	0%	(25)			0%	(19)

TABLE 4.20

Estimated Odds Ratios for Parental Occupation and Exposures
Comparing Cases and Random Sample Controls: Stratified Analyses

Factor	Pooled Odds Ratio	Maximum Likelihood Odds Ratio	Lower & Upper 95% Limit	Likelihood Ratio test	P	Mantel Haenszel Summary Odds Ratio	Mantel Haenszel Summary χ^2	P
Maternal Lead Exposure	2.30	2.48	0.81-7.54	2.48	p =.12	2.47	1.77	p =.18
Paternal Lead Exposure	1.67	1.61	0.99-2.59	3.72	p =.05	1.63	3.33	p =.07
Paternal Exposure to Paint with Lead	2.30	2.23	1.19-4.19	6.12	p =.01	2.29	5.67	p =.02
Paternal Exposure to Lead Smelting	1.88	1.78	0.90-3.51	2.72	p =.10	1.78	2.26	p =.13
Paternal job: Carpenter	3.59	4.65	1.29-16.82	5.55	p =.02	4.46	4.82	p =.02
Father employed by Company D	4.95	5.08	1.15-22.49	4.80	p =.03	5.16	3.79	p =.05
Paternal job: Factory	1.72	1.97	1.04-3.71	4.23	p =.03	1.988	3.78	p =.06

TABLE 4.21

Estimated Odds Ratios for Paternal Employment in a Factory:
Stratified Analyses With 3 Types of Strata

Type of Stratification	Maximum Likelihood Odds Ratios	Lower & Upper 95% Limit	Likelihood Ratio Test	P	Mantel-Haenszel Summary Odds Ratio	Mantel-Haenszel Summary χ^2	P
Hospital-Year of Birth	1.97	1.04-3.71	4.23	p =.03	1.988	3.78	p =.06
Hospital of Birth Only	1.92	1.05-3.54	4.28	p =.04	1.91	3.86	p =.05
Year of Birth Only	1.69	0.94-3.05	2.95	p =.09	1.70	2.57	p =.11

TABLE 4.22

Estimated Odds Ratios for Exposures by Severity of Case Lesion
Comparing Cases and Random Sample Controls

Severity[1] of Lesion	Factor	Pooled Odds Ratio	Maximum Likelihood Odds Ratio	Lower & Upper 95% Limit	Likelihood Ratio Test	P	Mantel Haenszel Summary Odds Ratio	Mantel Haenszel Summary Odds Ratio χ^2	P
Less severe	Paternal lead exposure	1.18	1.33	.61 - 2.91	.513	p =.47	1.34	.27	p =.60
	Maternal lead exposure	0.89	0.81	.08 - 7.84	.035	p =.85	0.82	.74	p =.71
More severe	Paternal lead exposure	2.06	1.75	.95 - 3.25	3.18	p =.08	1.85	2.69	p =.10
	Maternal lead exposure	3.56	4.95	1.14 - 21.50	4.87	p =.03	5.48	3.65	p =.05

(1) Less severe: Clinical exam and/or catheterization only performed on cases
(2) More severe: Surgery and/or autopsy performed on cases

TABLE 4.23

Estimated Odds Ratios for Paternal Occupations
by Severity of Case Lesion Comparing Cases and Random Sample Controls

Severity of Lesion	Factor	Pooled Odds Ratio	Maximum Likelihood Odds Ratio	Lower & Upper 95% Limit	Likelihood Ratio Test	P	Mantel Haenszel Summary Odds Ratio	Mantel Haenszel Summary Odds Ratio χ^2	P
Less severe	Paternal job Carpenter	1.88	2.03	0.33 - 12.47	0.55	p =.457	1.96	0.07	p =.794
	Paternal job Factory	1.91	2.23	0.80 - 6.23	2.26	p =.133	2.16	1.62	p =.203
	Exposure to Paint with Lead	1.73	2.33	0.81 - 6.73	2.36	p =.124	2.27	1.71	p =.191
More severe	Paternal job Carpenter	11.38	12.29	1.33 - 113.72	6.54	p =.010	11.76	5.09	p =.024
	Paternal job Factory	1.64	1.78	0.80 - 3.98	1.93	p =.164	1.84	1.46	p =.227
	Exposure to Paint with Lead	2.82	2.45	1.07 - 5.61	4.54	p =.033	2.65	3.85	p =.049

TABLE 4.24

Comparison of Odds Ratios for Parental Occupations and Exposures
Between Stratified Analysis and Matched Analysis

Factor	Stratified Analysis				Matched Analysis			
	Odds Ratio	Lower & Upper 95% Limit	Likelihood Ratio Test	P	Odds Ratio	Lower & Upper 95% Limit	Likelihood Ratio Test	P
Maternal Lead Exposure	2.48	0.81 - 7.54	2.48	p >.10	2.47	0.82 - 7.48	2.54	p >.10
Paternal Lead Exposure	1.61	0.99 - 2.59	3.72	p =.05	1.54	0.94 - 2.51	2.93	p >.05
Paternal Exposure to Paint With Lead	2.23	1.19 - 4.19	6.12	p <.03	2.62	1.33 - 5.16	7.88	p =.005
Paternal Exposure to Lead Smelting	1.78	0.90 - 3.51	2.72	p =.10	1.70	0.86 - 3.37	2.30	p >.10
Paternal Job: Carpenter	4.65	1.29 - 16.82	5.55	p <.03	3.84	1.08 - 13.70	4.38	p <.05
Paternal Job: Factory	1.97	1.04 - 3.71	4.23	p <.05	2.06	1.07 - 3.97	4.60	p <.05
Father Employed by Company D	5.08	1.15 - 22.49	4.80	p <.05	12.29	1.41 - 106.93	7.45	p $\leq$.01

TABLE 4.25

Paternal Employment as a Carpenter by
Case-Control Status for Maternal Smoking Groups

Maternal Smoking Groups	Paternal Employment	Cases	Random Sample Controls
Smoking 0-20 cigarettes per day	Carpenter	8	4
	Other	93	299
Smoking 21+ cigarettes per day	Carpenter	1	1
	Other	15	22

Mantel-Haenszel Summary Odds Ratio: 3.35
Mantel-Haenszel χ^2: 2.93 p =.09
χ^2 for heterogeneity: .54 p =.46

TABLE 4.26

Paternal Employment as a Carpenter by
Case-Control Status for Exposure to Paint with Lead and No Exposure

Paternal Exposure	Paternal Employment	Cases	Random Sample Controls
Exposure to Paint	Carpenter	4	2
	Other	17	27
No Exposure to Paint	Carpenter	2	3
	Other	84	272

Mantel-Haenszael Summary Odds Ratio: 2.66
Mantel-Haenszel χ^2: 1.45 p =0.23
χ^2 for heterogeneity: <.001 p =1.0

TABLE 4.27

Paternal Employment in a Factory by Case-Control Status for Exposure to Paint with Lead and No Exposure (1)

Paternal Exposure	Paternal Employment	Cases	Random Sample Controls
Exposure to Paint	Factory Worker	6	7
	Other	15	22
No Exposure to Paint	Factory Worker	15	27
	Other	71	248

Mantel-Haenszel Summary Odds Ratio: 2.12
Mantel-Haenszel χ^2: 4.24 p =0.04
χ^2 for heterogeneity: 3.75 p =0.99

(1) Data are evaluated over hospital strata within paint exposure category.

TABLE 4.28

Paternal Employment in a Factory by Case-Control Status for Maternal Smoking Groups (1)

Maternal Smoking Groups	Paternal Employment	Cases	Random Sample Controls
Smoking 0-20 cigarettes per day	Factory Worker	19	35
	Other	79	268
Smoking 21+ cigarettes per day	Factory	2	3
	Other	14	20

Mantel-Haenszel Summary Odds Ratio: 1.99
Mantel-Haenszel χ^2: 4.21 p =.04
χ^2 for heterogeneity: 4.82 p =.99

(1) Data are evaluated over hospital strata within smoking categories.

TABLE 4.29

Paternal Employment as a Factory Worker by Case-Control Status for Employment by Company D and Others (1)

Paternal Employer	Paternal Employment	Cases	Random Sample Controls
Worked for Company D	Factory Worker	3	2
	Other	2	1
Did not work for Company D	Factory Worker	18	35
	Other	89	282

Mantel-Haenszel Summary Odds Ratio: 1.79
Mantel-Haenszel χ^2: 2.80 p =0.09
χ^2 for heterogeneity: 4.38 p =0.99

(1) Data are evaluated over hospital strata within employer category.

TABLE 4.30

Paternal Exposure to Paint by
Case-Control Status for Maternal Smoking Groups

Maternal Smoking Group	Paternal Paint Exposure	Cases	Random Sample Controls
Smoking 0-20 cigarettes per day	Exposure to Paint with Lead	18	22
	No Exposure	74	260
Smoking 21+ cigarettes per day	Exposure to Paint with lead	3	7
	No Exposure	13	15

Mantel-Haenszel Summary Odds Ratio: 2.03
Mantel-Haenszel χ^2: 4.90 p =.03
χ^2 for heterogeneity: 4.21 p =.04

TABLE 4.31

Comparison of the Prospective and Retrospective Logistic Regression Model Using Maximum Likelihood Estimators:

Model: $\ln \left(\frac{y}{1-y} \right) = B_0 + B_1X_1 + B_2X_2 + B_3X_1X_2$

I. Retrospective Model

y = paint exposure (1 = exposure)

B_0 = constant

B_1 = case/control

B_2 = cigarette exposure (1 = >20 cigarettes per day)

B_3 = interaction cases + cigarette smoking

B_0	B_1	B_2	B_3
-2.46891	1.05362	1.55262	-2.00914

II. Prospective Model

y = Case/control

B_0 = constant

B_1 = paint exposure

B_2 = cigarette exposure

B_3 = interaction: paint exposure + cigarette exposure

B_0	B_1	B_2	B_3
-1.26493	1.05362	1.12183	-2.00914

TABLE 4.32

Multiple Logistic Progression Analyses of Exposure Variables Among Cases and Controls Using Retrospective and Prospective Models

Variable	Crude Odds Ratio	Retrospective Model Adjusted Odds Ratio	Prospective Model Adjusted Odds Ratio	Prospective Model 95% Confidence Interval	Likelihood Ratio Test	df	p value
smoking >20 cigarettes/day	2.03	1.74	2.88	1.21 - 6.85	8.6574(1)	3	p <.05
paternal job as a carpenter	3.59	6.09	5.60	1.26 - 24.99	5.086	1	p <.025
interaction of nausea and vomiting >6 mos. with maternal age >30	9.60	--	9.87	1.79 - 54.56	8.882(2)	3	p <.05
Low birthweight	5.46	6.19	6.07	2.88 - 12.81	21.3496	1	p <.001
paternal exposure to paint with lead	2.30	2.44	2.00	0.91 - 4.40	8.6574(1)	3	p <.05
paternal employment in a factory	1.72	1.80	1.73	0.85 - 3.52	2.1700	1	p >.10
paternal employment by Company D	4.95	--	3.04	0.57 - 16.25	-2.0244	1	--

(1) Because of the potential interaction between cigarette smoking and paint exposure, the likelihood ratio test is based on removing the cigarette smoking, paint exposure, and interaction terms.
(2) Because of the interaction with maternal age and nausea and vomiting the likelihood ratio test is based on removing these three terms.

TABLE 4.32 (Cont'd.)

Variable	Crude Odds Ratio	Retrospective Model Adjusted Odds Ratio	Prospective Model Adjusted Odds Ratio	Prospective Model 95% Confidence Interval	Likelihood Ratio Test	df	p value
nausea for ≥6 months of pregnancy	1.75	1.99	1.22	0.50 - 2.97	8.882(2)	3	p <.05
maternal age >30	2.30	0.98	0.80	0.35 - 1.82	8.882(2)	3	p <.05
overall maternal lead exposure	2.30	--	1.30	0.29 - 5.90	-2.0244	1	--
interaction of paint exposure and >20 cigarettes per day	0.49	--	0.522	0.08 - 3.51	8.6574(1)	3	p <.05

(1) Because of the potential interaction between cigarette smoking and paint exposure, the likelihood ratio test is based on removing the cigarette smoking, paint exposure, and interaction terms.
(2) Because of the interaction with maternal age and nausea and vomiting the likelihood ratio test is based on removing these three terms.

TABLE 4.33

Multiple Logistic Regression Analysis of Exposure Variables Among Cases with Severe Lesions and Controls Using Retrospective Model

Variable	Crude Odds Ratio	Adjusted Odds Ratio	95% Confidence Interval
Overall maternal lead exposure	3.56	3.13	0.78 - 12.42
Overall paternal lead exposure	2.06	1.75	0.91 - 3.37
Paternal employment as a carpenter	11.38	2.95	0.45 - 19.39
Paternal exposure to paint with lead	2.82	1.27	0.39 - 4.13