FAMILIAL RISKS OF ANENCEPHALY AND SPINA BIFIDA
IN BRITISH COLUMBIA

by

MARY LOUISE McBRIDE
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to the required standard

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Department of Medical Genetics

The University of British Columbia
2075 Wesbrook Place
Vancouver, Canada
V6T 1W5

Date October 5, 1977
ABSTRACT

The purpose of this study has been to assess the risk of central nervous system malformations to sibs of individuals born in British Columbia with either anencephaly or spina bifida cystica, two related central nervous system defects. Risks of anencephaly, spina bifida cystica, and other central nervous system anomalies were derived, both for all sibs and for subsequent sibs of the index case. The sex, type of malformation, parity, and type of birth (livebirth or stillbirth) of the index case were all considered in the estimation of sibling risk. In addition, various hypotheses regarding the aetiology of these malformations were discussed. An attempt was made to fit a model for polygenic inheritance to the data and to estimate the degree of genetic determination in the causation of these defects in the province.

Index cases of anencephaly and spina bifida cystica were ascertained from routinely-collected records on morbidity and mortality, obtained from the Division of Vital Statistics of the British Columbia Department of Health. All affected cases born in the province from 1952 to 1970 were considered probands. The family information was acquired using linked groupings of British Columbia marriage, birth and stillbirth records for the period from 1946 to 1970. The use of these records was intended to avoid biases in ascertainment of index cases and to provide complete family information.
The empiric risk of anencephaly or spina bifida cystica to all sibs of individuals born in British Columbia with either of these defects was 2.4%, about fifteen times the population incidence. The risk to subsequent sibs of the first affected individual in a family (2.1%) was not significantly different from the risk to all sibs. There was no difference in risk when the sex, type of malformation, parity, or type of birth of the proband were taken into account. Brothers and sisters of index cases had the same risk of either anencephaly or spina bifida cystica, and there were equal proportions of each defect among sibs. The risk of recurrence of either of these anomalies after two previously affected sibs was 4.8%, or approximately double the risk after one affected sib. No increased risk of any other central nervous system defect was observed in the families of the index cases.

The sibling risk of anencephaly and spina bifida cystica in British Columbia is much lower than that reported elsewhere. Comparison of the results of this study with other family studies of anencephaly and spina bifida cystica suggest that geographical differences in risk can be attributed largely to environmental factors in causation. The risk is, however, large enough to justify the continuation of amniocentesis service to mothers of children with anencephaly or spina bifida cystica. The linked family records available in British Columbia can be utilized further in order to study the sibling risks of recurrence of other congenital malformations in the province, in particular those with a higher frequency or those that present greater medical problems in the community.
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Chapter 1

INTRODUCTION

Anencephaly and spina bifida cystica (ASB) are two related severe congenital nervous system (CNS) defects. Several factors influence the population incidence\(^1\) of these malformations, including place of birth, sex, and ethnic group (see section 2.3.1). The aetiology of these anomalies is not clear, but family studies have indicated an increased risk of both conditions in subsequent siblings of affected individuals (Warkany, 1971).

The best available estimates of familial risks of anencephaly and spina bifida cystica come from empiric data collected in a number of centres in the United Kingdom (see section 2.4). However, there is some question that these estimates are valid for populations in other parts of the world. Furthermore, biases in the ascertainment of probands and in data collection lessen the reliability of the results of these studies (see section 2.4).

The purpose of the present study has been to assess the sibling risks of congenital central nervous system anomalies, among families who have had a child with anencephaly or spina bifida cystica born in British British Columbia during the years 1952 to 1970. These risks were determined

\(^1\)Throughout this paper, the term incidence has been used specifically to mean incidence at birth.
using routinely-collected records on morbidity and mortality, obtained from the Division of Vital Statistics of the British Columbia Department of Health, relating to the British Columbia birth population of those years. Risks of anencephaly, spina bifida cystica, and other congenital central nervous system defects were derived, taking into account the sex, type of malformation, and type of birth (livebirth or stillbirth) of the index case. Also, an attempt was made to fit a model for polygenic inheritance to the data and to estimate the degree of genetic determination in the causation of anencephaly and spina bifida cystica in the province.

The use of linked groupings of routinely-produced vital and health records as a database for the present study was intended to avoid the ascertainment biases found in previous studies on familial risks in anencephaly and spina bifida cystica. Record linkage is a procedure that brings together independently-derived records relating to the same individual or family; this can be done for the whole of a defined population. Specifically, it can be used to assemble, on a large scale, the health histories of family members in order to provide data on morbidity and mortality in family groups. Other family studies of neural-tube closure defects have not been able to obtain such comprehensive family histories.

It was felt that the data afford virtually complete ascertainment of cases born in British Columbia in the years 1952 to 1970. Furthermore, the linked family groupings, which include British Columbia marriage, birth, death, hospital and registry records, also provide complete family information relating to all births, both normal and abnormal, that have occurred in the province during the same period.
Chapter 2

BACKGROUND

2.1 The Malformations

Anencephaly is a lethal condition characterized by partial or complete absence of the brain, as distinct from encephalocele, another central nervous system anomaly in which the brain tissue is exposed through a defect in the skull. The term spina bifida refers to several midline defects of the osseous spine, some with neural involvement, and some without. Those vertebral defects that involve the meninges or neural tissue, of which there are several types, are collectively called spina bifida cystica. A defect that consists of a protruding sac filled with meninges and spinal fluid is called a meningocoele. If spinal nerves or cord are included in the protrusion, the defect is known as a meningomyelocele. Less common forms of spina bifida cystica include myeloschisis, in which the neural plate has failed to form a tube, and a rare form called myelocystocele. Spina bifida cystica is found most commonly in the lumbosacral area of the spine.

While anencephaly is invariably lethal at birth, only about 25% of spina bifida cystica cases are stillborn (Laurence, 1966). Without treatment, a further 14% of the total would be expected to die in the first week of life, and only 16% of total cases would survive to the age of one year. However, with surgical intervention, about 70% of liveborn cases are
saved, although most become handicapped (Rickham and Mawdsley, 1966).
Individuals with spina bifida cystica frequently suffer from "meningitis, hydrocephaly, paralysis and deformity of the lower limbs, and urinary bladder paralysis and its consequences" (Sharrard et al., 1963); there are more females with these complications than males. Anencephaly and spina bifida cystica constitute a significant proportion of the total infant mortality and morbidity in western countries; indeed, in Canada, anencephaly is "the most common congenital abnormality causing perinatal death" (Elwood, J.M., 1974).

The joint occurrence of anencephaly and spina bifida cystica ranges from 9% (Record and McKeown, 1949) to 17% (Frézal et al., 1964), a significantly higher proportion than would be expected if these two defects were unrelated. In addition, hydrocephaly is associated with about 80% of cases of meningomyelocoele (Lorber, 1961), as a result of secondary defects related to the Arnold-Chiari malformation (Buta, 1975). Its incidence is highest when the spinal defect is in the lumbar region (Lorber, 1961). Most studies (Elwood, J.M., 1976b) have not been able to demonstrate an association of ASB with any other congenital defect.

2.2 Embryology

The central nervous system in humans starts to differentiate morphologically with the formation of the neural plate on the dorsal surface of the three-week old embryo. This plate infolds to form the neural groove; the folds then fuse to form a tube, starting in the mid-dorsal region and extending both cranially and caudally to the anterior and posterior neuropores. This process is completed by the fourth week of development (Nakano, 1973;
Corliss, 1976). At this stage the neural structure consists of a long tube (which develops into the spinal cord) with a broader cephalic end (the future brain). In the meantime, mesoderm has completely surrounded the neural tube and separated the neuroectoderm from the ectoderm.

Both anencephaly and spina bifida cystica probably result from a failure of fusion of the neural folds during embryogenesis (Laurence, 1964; Nakano, 1973), and consequently these defects are present as early as the fourth week of development. It is interesting to note that, while anencephaly is caused by a failure to fuse at the anterior end of the embryo, and most spina bifida cystica lesions are found near the posterior end of the spinal cord, relatively few defects are discovered in the mid-dorsal region. This observation suggests that there may be a very specific time during which the defects can occur. Alternatively, more severe manifestations of the defect may be lost early in pregnancy, and consequently not even recognized. Both abnormalities are obvious at birth.

2.3 Epidemiology

Epidemiological studies of anencephaly and spina bifida cystica have revealed many positive associations, some with a possible genetic basis (sex, ethnic group, family) and others that are suggestive of environmental factors (place of birth, secular and seasonal trends). Demographic variation in the incidence of these conditions can be divided into two types: variation in populations and variation within families. The epidemiological aspects of the incidence of ASB are summarized in Table I; these significant associations are described more fully below.
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²Parity: the number of viable births carried by a particular woman.
2.3.1 Variation in Populations

**Place:** The overall incidence of ASB is approximately two per thousand total births (Warkany, 1971), but the geographical variation is considerable. For anencephaly the highest rates (>1 per 1000 births) are found in the British Isles, northeast North America, and the Middle East as far as India (Leck, 1974), with exceptionally high figures (>3 per 1000 births) being recorded in Ireland, Scotland, the north and west of Britain, Alexandria, Egypt, and among the Sikhs of India (Leck, 1974). The incidence is generally low (<0.6 per 1000 births) in Asia, Africa, and South America, while most of the United States and Canada, Europe and Israel have intermediate rates (Nakano, 1973). There is a sixty-fold difference between the lowest reported incidence of anencephaly, in Bogota (0.11 per 1000 births) (Stevenson et al., 1966) and the highest, among the Sikhs (6.5 per 1000 births) (Searle, 1959). The incidence of spina bifida cystica is similar to that of anencephaly except in Oriental countries, where the rate of spina bifida cystica is very much lower than that of anencephaly (Leck, 1974).

There are indications of both a north-south and an east-west gradient in the incidence of neural-tube closure defects in North America. The rates in the eastern part of the continent are one and one-half to three times those in the west (Elwood, J.M., 1976a), while the figures in the north show a two and one-half-fold increase over those in the south (Alter, 1963). Among Canadian provinces, the incidence of ASB declines steadily from New Brunswick on the east coast, where the rate is 4.0 per thousand total births, to British Columbia in the west, where the incidence is only 1.5 per thousand total births (Elwood, J.M., 1974). In fact, the population of British Columbia has one of the lowest rates of ASB among Caucasian populations (Elwood, J.M., 1974).
Ethnic Group: Racial background is another demographic variable that shows a strong relationship to the occurrence of neural-tube closure defects. The incidence of anencephaly and spina bifida cystica is high among Sikhs, and relatively low among blacks and Ashkenazi Jews, wherever members of these groups reside (Leek, 1974). This implies that there may be some genetic differences in predisposition among these groups. However, the incidence among Caucasians shows marked geographical variation (Leck, 1972), implicating environmental factors that vary with place of residence. For instance, the English in Quebec have a lower rate of neural-tube closure defects than those in Britain, while the incidence among the French in Quebec is higher than that in France (Horowitz and McDonald, 1969). Alternative explanations have been proposed for both these phenomena; the constant rates among people of Mongoloid, Negroid, or Latin American origin could be due to maternal factors rather than a genetic susceptibility to the disease itself; and selective migration could lead to genetic differences among Caucasians living in different areas of the world (Leck, 1974).

Secular Variation: Complicating the pattern of geographical variation in incidence of neural-tube closure defects are changes in incidence that have occurred through time, in many parts of the world. However, not all areas have shown this type of variation; and furthermore, the trends observed have not been consistent from place to place or through time. For instance, a gradual rise in the frequency of each defect, followed by a decline in incidence to the original level, occurred in Berlin from 1945 to 1950, in Birmingham from 1950 to 1965, and in England and Wales as a whole in the period from 1920 to the 1940's (Rogers and Morris, 1971). Scotland (Leck
and Rogers, 1967) and Ireland (Elwood, J.H., 1970) showed similar, though not identical trends, to those in England. The incidence of ASB in New England rose dramatically between 1920 and 1935, culminating in a rate for the years 1929 to 1932 more than three times that preceding or following the epidemic period (MacMahon and Yen, 1971; Janerich, 1973).

Canadian data show a gradual decline in incidence of ASB since 1950, except for an increase in spina bifida cystica rates between 1960 and 1962 (Elwood, J.M., 1974). The rate of anencephaly mortality in Ontario declined most dramatically of all the provinces, whereas the rate for Quebec peaked around 1954 and then decreased. Mortality rates for anencephaly in the Prairies and the Maritimes declined more slowly, with increases in 1958 in the Prairies, and 1956 in the Maritimes. There was a large decrease in anencephaly mortality rates in the Maritimes in 1967. The rate in British Columbia has remained constant since 1950, except for a small peak in 1952. Such trends are indicative of environmental influences, and the consistently low rate in British Columbia would suggest that, if environmental factors are affecting the incidence of ASB in the province, their effect has been constant through time (Elwood, J.M., 1974).

**Seasonal Variation:** The effect of season on the incidence of neural-tube closure defects varies considerably with year and locality. Significant seasonal variations have been found in the British Isles (Leck, 1974), and in Canada (Elwood, J.M., 1976a), although not in the United States (Elwood, J.M., 1974) or in Europe (Leck, 1974). However, the seasonal differences have not been consistent for either anencephaly and spina bifida cystica, varying with time and between populations (Leck, 1974).
A relationship between season and incidence of neural-tube closure defects has been established for the four Canadian provinces of British Columbia, Alberta, Manitoba, and New Brunswick from 1966 to 1969 (Elwood, J.M., 1976a). The combined incidence of anencephaly and spina bifida cystica in these provinces varied from 2.19 per thousand total births in the three-month period from March to May, to 1.77 per thousand total births from June to August and from December to February. This type of variation also suggests some environmental agent affecting the incidence of neural-tube closure defects.

**Socio-Economic Status:** Socio-economic factors have a pronounced effect on the incidence of ASB, in most areas of the world. A higher incidence of neural-tube closure defects has been reported for those in the lower socio-economic groups, while rates among those of more prosperous socio-economic status are relatively low, although the extent of the differences among groups is variable (Nakano, 1973; Leck, 1974). This association has also been observed in Canada (Horowitz and McDonald, 1969; Elwood, J.M., 1976a). It has not been found, however, in Hungary, Israel, or among blacks (Nakano, 1973; Leck, 1974).

**Environment:** In an effort to identify some of the environmental influences on the development of central nervous system anomalies, several attempts have been made to correlate the incidence of these defects with various factors known to influence other conditions. Infections and other illnesses, chemicals in diseased potatoes, minerals in drinking water, and drugs that cause folate depletion are just a few of the many substances that have been examined recently in terms of their relationship to anencephaly.
and spina bifida cystica (Leck, 1974). The correlation with potato blight seems to have been spurious (Leck, 1974), and no relationship to specific illnesses has been found (Nakano, 1973). Research into environmental agents is continuing.

2.3.2 Variation within Families

**Maternal Age and Parity:** The combined effects of maternal age and parity result in marked differences in the incidence of both anencephaly and spina bifida cystica, although the effect of age is less than that of parity, and the extent of the variation differs considerably among countries (Nakano, 1973). A low incidence among second births has been observed in all studies of ASB, and most places report an increase in incidence with parity greater than two. The frequency among first births is low in Israel, but high in most other areas, including North America (Leck, 1974). Several studies, including one Canadian study, describe a U-shaped distribution of incidence with parity (Ingalls *et al.*, 1954; Record, 1961; Naggan and MacMahon 1967; Elwood, J.M., 1976a). In Britain, incidence varies with the combined influence of age and parity, being highest in firstborns to both young mothers and mothers over 35. A trend towards increased rates with increasing maternal age has been observed in most studies, although in Israel and Britain this only occurs among primaparae. However, in cohort studies in New York (Janerich, 1971; Janerich, 1972) and in Canada (Elwood, J.M., 1976a), the incidence of ASB was shown to decrease with increasing age. This implies that the U-shaped associations with parity may be merely a result of a cohort effect, since the parity groups have different proportions of women of each age.
**Sex Distribution:** There are striking differences in the incidence of ASB between the sexes. The incidence of neural-tube closure defects in females is much higher than that in males, in western countries; in Oriental populations, a sex difference is not apparent (Leck, 1974). For anencephaly, the ratio of males to females varies considerably with locality, from 0.45:1 in the British Isles to near unity in Oriental countries; while that for spina bifida cystica is fairly constant at approximately 0.75:1 (Leck, 1974). The proportion of females is greater among stillbirths than among liveborn infants.

It has been noted that the incidence of ASB among males is generally more stable over time than that among females (Leck, 1974). In Canada, the ratio of males to females with anencephaly from 1943 to 1970 is 0.46:1 (Elwood, J.M., 1974), with a barely significant increase in the proportion of males within that time period (Elwood, J.M., 1976a).

**Twin Studies:** If the production of neural-tube closure anomalies was influenced by factors in the intra-uterine environment, one would expect a higher incidence of ASB among twins than among non-twin siblings of affected cases. Furthermore, a genetic influence on the development of ASB would result in a greater proportion of monozygotic than dizygotic twins concordant for a neural-tube closure defect. In fact, concordance for ASB among twins seems to be uncommon; the proportion of affected among twins (2.8%) is lower than that reported among sibs (3% to 6%) (Elwood, J.M., 1976b). However, the observed concordance rate among twins is not incompatible with a postulated risk as high as 6% (Elwood, J.M., 1976b). The number of twins among individuals affected with ASB is only slightly lower than expected in the general
population (Elwood, J.M., 1976b), suggesting that concordance does not result in greatly increased foetal loss. Unfortunately, the zygosity of observed concordant twin pairs has not been reported. However, a normal ratio of like-sexed to unlike-sexed concordant twin pairs is found, implying that zygosity does not affect concordance. This also suggests that the lower recurrence risk in twins may be related to the twinning process itself, perhaps due to an increased risk of early abortion in concordant twin pairs.

**Sibling Risks:** Increased risks to siblings of individuals affected with ASB are of three kinds; first, the risk of abortion and stillbirth; second, the chance of developing spina bifida occulta, a spinal defect involving the vertebrae only; and third, the risk of another neural-tube closure defect (Leck, 1974). Apart from the increased incidence of hydrocephaly associated with spina bifida cystica, there seems to be no increased risk of any other types of congenital malformations among sibs.

Higher rates of abortion and stillbirths in mothers with affected children have been reported (McDonald, 1971; Richards, 1973); however, such data are open to bias because of difficulties in ascertainment of pregnancy loss and therefore are hard to assess. Studies that show an increase in the proportion of affected foetuses (Nishimura, 1970; Alberman et al., 1973) from lost pregnancies have led to suggestions that such differential loss may contribute to the geographical differences in incidence and to the increased rate among firstborns, although not to the seasonal and socio-economic differences, nor to the variation with higher maternal parity and age (Leck, 1974).
The information on an increased liability to spina bifida occulta is also difficult to quantify, due to the difficulty in assessing its prevalence in the general population.

One of the more important risks to sibs of affected children is that of an increased susceptibility to ASB. A more detailed account of the extent and significance of sibling risks of neural-tube closure defects is given in section 2.4.

Other Family Studies: There have been several studies that have examined the risks of neural-tube closure defects among family members other than sibs. The risk to half-sibs of affected individuals is significantly increased (Leck, 1974); moreover, it seems to be greater for maternal than paternal half-sibs. In studies of cousins, only those on the maternal side showed an increased incidence (Carter and Evans, 1973). This maternal influence, however, may only be due to ascertainment bias, since information from the maternal side of the family is likely to be more complete.

2.4 Sibling Risks of Anencephaly and Spina Bifida Cystica

The calculation of the risks of other neural-tube closure defects in sibs of children with anencephaly or spina bifida cystica is an important aspect of the study of these conditions, both from the point of view of family counselling and in studies of aetiology. Estimates of the risk to sibs of either anencephaly or spina bifida cystica have varied from 1.4% (Naggan, 1971) in Israel from 1958 to 1968, to 6.1% (Lorber, 1965) to sibs of spina bifida cystica cases from a hospital series in Sheffield. The variation in risks to sibs among nine studies carried out since 1960 (see
<table>
<thead>
<tr>
<th>Locality</th>
<th>No. Propositi</th>
<th>No. Sibs</th>
<th>% Affected</th>
<th>Population Incidence per 1000 births</th>
<th>Source of Propositi</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel</td>
<td>776</td>
<td>--²</td>
<td>1.34</td>
<td>1.46</td>
<td>death and hospital records</td>
<td>Naggan, 1971</td>
</tr>
<tr>
<td>New York</td>
<td>139</td>
<td>308</td>
<td>3.24</td>
<td>2.00</td>
<td>birth, stillbirth, hospital records</td>
<td>Milham, 1962</td>
</tr>
<tr>
<td>London</td>
<td>870</td>
<td>1484</td>
<td>4.5</td>
<td>2.95</td>
<td>mortality data, hospital records</td>
<td>Carter and Evans, 1973</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>1095</td>
<td>1263</td>
<td>4.6</td>
<td>4.46</td>
<td>hospital records</td>
<td>Yen and MacMahon, 1968</td>
</tr>
<tr>
<td>Southampton</td>
<td>101</td>
<td>191</td>
<td>5.6</td>
<td>5.17</td>
<td>birth and hospital records</td>
<td>Williamson, 1965</td>
</tr>
<tr>
<td>Glasgow</td>
<td>318</td>
<td>904</td>
<td>5.6</td>
<td>5.6</td>
<td>vital records</td>
<td>Richards et al., 1972</td>
</tr>
<tr>
<td>Liverpool</td>
<td>1338</td>
<td>1790</td>
<td>3.9</td>
<td>6.5</td>
<td>mortality data, registry</td>
<td>Smithells et al., 1968</td>
</tr>
<tr>
<td>South Wales</td>
<td>829</td>
<td>1562</td>
<td>5.2</td>
<td>7.67</td>
<td>mortality data</td>
<td>Carter et al., 1968</td>
</tr>
<tr>
<td>Sheffield³²</td>
<td>722</td>
<td>1256</td>
<td>6.1</td>
<td>--</td>
<td>hospital records</td>
<td>Lorber, 1965</td>
</tr>
</tbody>
</table>

¹since 1960
²number not given in paper
³spina bifida cystica propositi only
Table II) can be attributed sometimes to incomplete ascertainment and followup of families, and sometimes to genuine differences in the populations studied. Three studies (Lorber, 1965; Carter and Roberts, 1967; Smithells et al., 1968) examined the risk after two affected children, and reported rates much greater than 6%.

The differences in incidence among sibs are not nearly as great as the variation in the population incidence of these defects. There is a tendency for the risk to be higher proportional to the population incidence in areas of low prevalence than in areas of high prevalence. Thus, in London (Carter and Evans, 1973), where three thousand total births are affected with anencephaly or spina bifida cystica, the risk among sibs is fifteen times that in the general population, or 4.5%; and in South Wales (Carter et al., 1968), which has 7.7 per thousand births affected, the incidence among sibs is 5.2%, or seven times the population risk.

In general, the lower the incidence of anencephaly and spina bifida cystica in the study population, the lower the risk of occurrence of the defects among sibs. Excluding the Israeli study (Naggan, 1971), which almost certainly gives an underestimate of the true risk since it excludes some affected sibs, the lowest reported risk, of 3.2%, occurs in New York (Milham, 1962). The highest risks to sibs (5.2% to 5.6%) are found in Southampton (Williamson, 1965), Glasgow (Richards et al., 1972) and South Wales (Carter et al., 1968), with a relatively high incidence of ASB (over five per thousand births). The more moderate risk among sibs in Liverpool (Smithells et al., 1968) of 3.9% is an exception to this pattern since the incidence of neural tube closure defects there (6.5 per 1000 births) is quite high. All four of these series were based on vital and hospital records, family information was obtained in every case through home visits,
and the study periods were overlapping, so the difference between the Liverpool study and the others can be regarded as real. The only other recent American study was in Rhode Island (Yen and MacMahon, 1968), where both the population incidence (4.5 per thousand births) and the proportion affected among sibs (4.6%) were somewhat higher than in New York.

In Glasgow (Richards et al., 1972) and in London (Carter and Evans, 1973) the risk of a neural-tube closure defect in sibs of anencephalic cases was elevated over that for patients with spina bifida cystica, although not significantly so in the London study. In two other series, in Liverpool (Smithells et al., 1968) and Rhode Island (Yen and MacMahon, 1968), no difference was seen and in Southampton (Williamson, 1965) and South Wales (Carter et al., 1968) the risk was actually slightly higher among sibs of spina bifida cystica index patients. In most studies the neural-tube closure defects seen in the sibs were more often the same as those in the propositi; one study (Yen and MacMahon, 1968), that considered subsequent sibs only, did not observe this pattern.

The sex difference in incidence that is observed in population studies of anencephaly and spina bifida cystica is also found among sibs of these patients. Studies in South Wales (Carter et al., 1968), Glasgow (Richards et al., 1972), and London (Carter and Evans, 1973) all had a higher proportion of females than males among their index patients, this difference being greater in all cases among the anencephalic probands than among the spina bifida cystica index cases. All except the Glasgow series also reported an increased risk to female sibs of their index patients. The London study reported a particularly high risk among female sibs of female anencephalic probands, while the survey in South Wales found an increased risk in all female sibs except those of female spina bifida cystica propositi. An
increased risk to female sibs was also observed in Southampton, but the series was too small to be analyzed by sex or malformation of the propositus. The Glasgow survey was unusual in that the risk to male and female sibs of male index cases was the same, and the risk to male sibs of female probands was slightly above that of sisters of female index cases. When the data were broken down by malformation, however, it was observed that there was an increased risk to female sibs of female spina bifida cystica cases, but that the risk to sibs of anencephaly probands was elevated for those of the same sex as the proband.

The risk of malformations other than anencephaly and spina bifida cystica to sibs of affected individuals did not seem to be increased over the general population levels, although an increase in foetal loss was observed in Southampton (Williamson, 1965) and one hospital series in Sheffield (Lorber, 1965) reported an increase in hydrocephaly among sibs of spina bifida cystica patients.

In discussion of the sibling risks of anencephaly and spina bifida cystica, a distinction must be made between the incidence among all sibs of affected children, which is the risk that has been quoted above, and the risk to subsequent sibs, which is the risk used for most counselling purposes. Studies in Southampton (Williamson, 1965), South Wales (Carter et al., 1968), Glasgow (Richards et al., 1972), and London (Carter and Evans, 1973) examined the risk to sibs both before and after the index patient, and found no difference in incidence among sibs between the two groups. However, an increase in risk to subsequent sibs of affected index cases was reported in Liverpool (Smithells et al., 1968), and in the family study of spina bifida cystica at Sheffield (Lorber, 1965). The recurrence risk was also
found to be greater in younger sibs of first-born cases of ASB, in Glasgow (Richards *et al.*, 1972).

The risk of recurrence of neural-tube closure defects after two affected sibs is also important in genetic counselling. Studies in Liverpool (Smithells *et al.*, 1968) and in Sheffield (Lorber, 1965) reported very high incidence rates among sibs following two cases of ASB (over 50%); however, it is difficult to put confidence in these estimates since both samples were small and biased in favour of high-risk families. A more reliable estimate is given by a British study (Carter and Roberts, 1967) that followed up 113 families with at least two affected cases. Out of 69 subsequent sibs in 47 families, eight children, or 12%, also had anencephaly or spina bifida cystica. The risk of either malformation was the same. The study concluded that risk of a recurrent neural-tube closure defect after two affected cases was about double the risk after one affected child had been born. Since sibling risks vary among areas with different incidence rates, it may be that the recurrence risk after the birth of two sibs with ASB varies significantly also.

2.5 Aetiology

2.5.1 Genetic Hypotheses

The influence of genetic factors in the causation of neural-tube closure defects is suggested by the observation of an increased frequency of the conditions among the relatives of affected individuals. However, family studies have also shown that the disease is not inherited in a simple Mendelian manner.
The most widely accepted genetic model of the aetiology of ASB is that of polygenic inheritance with a threshold effect. In the case of anencephaly and spina bifida cystica, this model assumes that a number of genes are acting additively in the development of the neural tube. This produces a normal distribution of liability to malformation in the population, with a threshold above which a defect is produced (Figure 1). In relatives of affected individuals, the mean liability is shifted upwards (Figure 1); therefore a higher percentage of relatives will have genotypes that are above the threshold.

The polygenic threshold model can be used to estimate the degree of genetic determination in these malformations, that is, the variation between individuals that can be attributed to genetic differences (Falconer, 1965). The degree of additive genetic variance, as a proportion of the total phenotypic variance (genetic and non-genetic), can be calculated. This proportion, known as the heritability, has been used as a minimum estimate of the degree of genetic determination.

There are several consequences of the polygenic threshold model (Carter, 1969). First, the risk of recurrence of the defects would be greater in relatives than in the general population, and higher in first-degree relatives than in more remote relations. Second, in areas of high incidence, the risk to sibs would be higher in absolute terms than the risk in areas of low incidence, but lower in proportion to the population incidence. Third, the recurrence risk should increase the greater the number of affected individuals in the family. All of these predictions are corroborated in family studies.
Liability in Population

![Distribution of liability for polygenically inherited conditions.](image)

Liability among Relatives

![Distribution of liability for polygenically inherited conditions.](image)

Figure 1: Distribution of liability for polygenically inherited conditions.
One consequence of the polygenic model seems to be contradicted by empirical evidence. Since the incidence of ASB is greater among females than among males, the polygenic model implies that affected females have a lower threshold of susceptibility, and therefore the risk for their sibs should be lower than that for brothers and sisters of affected males. In fact, family studies show that the highest risk is often among sisters of affected females. It may be that males actually do have an increased susceptibility to neural-tube closure defects, and also are more severely affected than females, being lost early in pregnancy. This suggestion is compatible with the observed sex differences in sibling risks as well as the female preponderance in the general population.

Edwards (1960) has shown that the overall risk to sibs in conditions inherited in this manner is approximately $\sqrt{p}$ when $p$, the population incidence, is between 0.1% and 1%. Other researchers (Smith, 1971; Curnow, 1972) have extended this analysis to determine the theoretical risks to sibs in a wide range of specific family situations. The recurrence risks for anencephaly and spina bifida cystica in various types of families has been estimated (Bonaiti-Pellé and Smith, 1974), using data on the population incidence and overall risks to sibs of these two defects in London (Carter and Evans, 1973). However, the confidence intervals for these estimates are very large (Smith, 1971) and their usefulness is consequently reduced considerably.

An alternative genetic hypothesis is the suggestion that anencephaly and spina bifida cystica may be inherited through maternal cytoplasm (Nance, 1969). A higher reported risk of ASB among maternal half-sibs of affected individuals than among paternal half-sibs, and an increased proportion of affected individuals among matrilineal relatives, have been cited
as evidence for cytoplasmic inheritance. This could explain the low concordance rate among twins, but pooled data from three studies (Carter et al., 1968; Yen and MacMahon, 1968; Carter and Evans, 1973) show that the difference in risk between maternal and paternal half-sibs is not significant. Furthermore, cytoplasmic inheritance has not been demonstrated so far in man.

Another alternative to the polygenic model is the concept of foetus-foetus interaction (Knox, 1970), which suggests that every singleton birth of anencephaly is the result of an early (implantation stage) immunological reaction between dizygous twins, in which one twin is killed and the other left with a neural-tube closure defect. This idea is supported by the fact of a correlation between dizygotic twinning rates and incidence of anencephaly around the world (Stevenson et al., 1966), and the relatively low concordance rate among twins, who according to this hypothesis are actually the result of triplet conceptions. Unfortunately, this hypothesis does not explain how an immunological interaction in very early embryogenesis would cause a systemic defect such as ASB that apparently occurs in the third week of embryological development. Also, this hypothesis cannot account for the higher female preponderance of affected cases in areas of higher incidence, or the increase in incidence with birth rank greater than two.

2.5.2 Other Hypotheses

The associations of neural-tube closure defects with time, place, socio-economic status, and maternal parity and age all suggest environmental factors influencing the development of these abnormalities. Despite a great deal of descriptive investigation, however, no specific factors have been conclusively identified, and certainly none of the common environmental agents
(drugs, viruses, chemicals) has been shown to be involved in the causation of these anomalies. Possibly the effects of environmental factors are also small and cumulative (Leck, 1974).

Descriptive and family studies of anencephaly and spina bifida cystica over the last twenty-five years have revealed a great deal of information about how the incidence of these conditions varies, but unfortunately have provided few insights as to why this variation occurs. Anencephaly and spina bifida cystica must have similar aetiologies, since they show similar patterns of variation in incidence, and also show increased risks of either anomaly in siblings of affected individuals. Furthermore, there is evidence for both environmental and genetic factors influencing the development of these defects. The increased incidence of neural-tube closure defects in the families of affected individuals, and the variation in incidence among different ethnic groups both suggest genetic involvement; and yet the low concordance rate among monozygotic twins and the associations with time, place, and maternal factors imply the operation of environmental factors as well.

What is not known is the extent of these two influences in determining neural-tube closure defects. Both genetic and environmental factors must be complex, since there is no situation in which more than a small proportion of children is affected, even that of monozygotic twins who share both the same genetic constitution and the same intra-uterine environment (Leck, 1974). That this situation should exist seems entirely reasonable, given the complexity of the developmental processes of the central nervous system.

At present neither environmental nor genetic hypotheses can provide accurate estimates of familial risks of anencephaly and spina bifida cystica. The best estimates of these risks, therefore, come from empiric data.
Chapter 3

MATERIALS AND METHODS

3.1 Data

3.1.1 Ascertainment of Cases

Index cases of anencephaly and spina bifida cystica were ascertained from vital records of stillbirth from the Division of Vital Statistics of the Department of Health in British Columbia, and from records of live-born children with congenital malformations retrieved from the register for handicapped children and adults of the British Columbia Health Surveillance Registry. The register itself acquires its cases through voluntary registration of affected individuals and through routine surveillance of British Columbia vital and hospital records (Lowry et al., 1975). The study covered births from 1952 to 1970, since it was for those years that both computerized vital and register records were available.

During the study period there were 678,401 livebirths recorded in the province. The definition of stillbirth changed in 1963 so that from 1952 to 1962, a total of 4,326 stillbirths from twenty-eight weeks gestation were recorded, and from 1963 to 1970, there were 3,599 stillbirths of twenty weeks gestation or more.

Because of the severity of the conditions, it is reasonable to assume that ascertainment from the above sources was virtually complete
(Trimble and Baird, 1977a). Individuals with both anencephaly and spina bifida cystica were categorized as anencephaly; those with spina bifida cystica and hydrocephaly were classed as spina bifida cystica.

3.1.2 Ascertainment of Families

The families of index cases were ascertained through computer linkage of records of the probands with files of vital records of marriage and birth that had been compiled into family groups (if the marriage record was available) or sib groups (if no marriage record was available).

The records of marriage, live- and stillbirth in these family files came also from the Division of Vital Statistics of the British Columbia Department of Health. The marriage records pertained to all British Columbia marriages and births from 1946 to 1970. Only births that occurred from 1952 to 1970 were considered in this study. There were over a million records in the linked marriage-to-birth and birth-to-birth files, all in alphabetical order by coded surname - about 52,000 records per letter of the alphabet.

These records had already been grouped into families or sibships by Trimble and Uh (1977) using record linkage techniques developed largely by Newcombe (Newcombe, 1967). This technique matched several items of identifying information found on both marriage and birth records, the most important of which was a double "soundex" code for the surname and maiden surname of the parents of the index case. All the records with a particular double soundex code constituted a "pocket." In the marriage-to-birth file, the marriage records preceded the birth records within each pocket. The birth records were ordered by birthyear and birth registration number.
Family or sibship groups were identified through "flags" at the end of each record.

The strength of the linkage to the family or sib groups was indicated by a specific value, the linkage weight, that was assigned to each birth record. It has been estimated that, with a linkage weight of eight, none of the records represent false linkages and that a maximum of 1.8% of true links are missed. The only families left out of these files are those with the surname combinations Singh-Kaur or Kaur-Kaur; the programme was not able to reliably discriminate separate families among all the marriage and birth records with these surname combinations.

3.1.3 Information

The study base consisted of register records and vital records of livebirth, stillbirth, and marriage. Two types of information available on these records were used in this study: first, identifying information, required for linkage of the records of the index cases to those in the family files; and second, descriptive data that were utilized in the analyses.

Information on the index cases of anencephaly and spina bifida cystica was recorded in revised ill-health summary (abbreviated "summary") format. The vital records of the family failes were in marriage index and birth index formats respectively. A double soundex code for the surname and maiden surname of the parents of the index cases was present on all three records. The marriage and birth index records had been coded for double soundex by The University of British Columbia by Trimble (Trimble and Uh, 1977); the ill-health summaries had been soundexed by Newcombe.2

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2H.B. Newcombe, Head, Population Research Branch, Chalk River Nuclear Laboratories, Chalk River, Ontario KOJ 1JO.
Specific details of birth were also available on both ill-health summaries and birth index records and were used in the linkage procedure. These included the type of birth (livebirth or stillbirth), the birthyear, and the birth registration number. The linkage weight, recorded on each birth record, was used as a check on the strength of the linkage of that record to the family or sib group.

The data used in the analysis of cases was retrieved mainly from the summary records, and included information on the type of malformation, the type of birth, the birth date, and the sex of the child.

The congenital malformation was originally documented on the vital records using the codes listed in the coeval International Classification of Diseases (I.C.D.) or International Classification of Diseases, Adapted (I.C.D.A.). These codes were revised on the register records as follows:

All those cases with anencephaly with or without any other congenital defect (except spina bifida cystica) were given one code.

All cases with anencephaly and spina bifida cystica together were given one code.

Spina bifida cystica without hydrocephaly was given a specific code, and spina bifida cystica with hydrocephaly was given another code.

Other congenital defects of the central nervous system and multiple CNS defects excluding anencephaly and spina bifida cystica were separate codes.

Because the stillborn index cases were ascertained from vital records and not register records, it was necessary to re-code the data on the type of malformation when reformatting the stillbirth records.

The linkage procedure itself made available a further piece of information - the parity of the mother. Since the dates of all births were
documented in the files, information on the number of viable sibs before and after the index case was immediately available.

This study is part of the Record Linkage Project being carried out at The University of British Columbia. Access to all records was subject to appropriate restrictions to ensure confidentiality of data.

3.2 Procedures

3.2.1 Retrieval

The original records for the study came from two sources. The liveborn index cases were ascertained from the records of the provincial register for handicapped children and adults, in ill-health summary format. Data on each case was contained in a header record, and there were a variable number of records pertaining to vital documents of death, documents of registration, and hospital admissions. Stillbirth cases were ascertained from computerized revised vital records of stillbirth.

The provincial register has routinely surveyed vital records of livebirth since its inception in 1952, but stillbirth records were not included in its surveillance system until 1964. Therefore the records of affected stillbirths were duplicated in the files of vital documents and in the register from 1964 to 1970. It was decided that the retrieval of all stillbirth cases, from 1952 to 1970, from the vital records would result in the greatest accuracy.

The first step was to retrieve the records of all children with central nervous system defects born in British Columbia from 1952 to 1970. From the file of all register cases born in the years 1946 to 1970, ordered by
date of birth, those cases with central nervous system anomalies born from 1952 to 1970 were selected. A file of stillborn cases with central nervous system defects born from 1952 to 1970 was already available in order of date of birth. The malformation code on these stillbirth records was altered; and the surnames were soundexed. The resulting files contained all the index cases of anencephaly and spina bifida cystica, and cases of other central nervous system anomalies, some of which were sibs of anencephalic or spina bifida cystica children.

The ill-health summary format was then revised to include only the information to be used in the study, and the stillbirth records were reformatted to correspond with those for livebirths.

The third step consisted of merging the two files containing the livebirth and stillbirth records. The merging process was accomplished in two steps. First, the two files were sorted, by double soundex code, control code (for type of birth), birthyear, and birth registration number. They were then merged into one file, preserving their sorted order. The order of the new file corresponded to that of the family files. This would make the subsequent retrieval process easier and faster.

The records of the index cases, coded for anencephaly and/or spina bifida cystica, were then separated from those that coded for other CNS defects. The retrieval of index cases from the family files could then proceed.

The retrieval procedure consisted of searching the family files for the birth record of each index case. All of the records pertaining to the family of the index case were then identified and extracted from the file.
Except for records with the surname combination Singh-Kaur or Kaur-Kaur, every index case should have linked to a birth record in either the marriage-to-birth file or the birth-to-birth file. Each summary record was first tested against the birth records in the marriage-to-birth file; then, if a link was not found, it was tested against the birth records in the birth-to-birth file. The resulting output grouped the records into families or sibships, with the summary records following the marriage and birth records, and with a family number assigned to each group.

It was decided to keep false linkages to a minimum. When the family files had originally been linked, all of the false links had been found in records with linkage weights of seven or less. Therefore the threshold for a true link in this study was set at eight. With this threshold, there should have been no false links.

After the linkage of summary records and family files was accomplished, the resulting file was searched for birth records that corresponded to a summary record of a birth with a CNS malformation other than anencephaly or spina bifida cystica. When a match was found, that summary record was labelled with the family number and added to the file as the last record in the family group.

The final file consisted of all British Columbia marriage and birth records of families with British Columbia-born anencephaly and spina bifida cystica cases, and summary records specifying all the central nervous system malformations among recorded births.
3.2.2 Analyses

Because the selection of affected individuals was through vital and register records, each index case was ascertained independently. Ascertainment was considered to be virtually complete, since the nature of the two conditions studied makes it unlikely that any cases would be missed or misdiagnosed. Therefore, when calculating the risk for all sibs of an affected individual, every case of anencephaly and/or spina bifida cystica was considered to be a proband, and each family was counted as many times as there were probands in the family. To assess the recurrence risk after one affected sib, only the first case in each family was identified as a proband, and all sibs born after the first affected case were counted. And, to assess the risk after two affected sibs, all births subsequent to the proband, designated the second affected birth in a family, were counted.

The analyses were designed to answer the following questions.

What are the empiric sibling risks for anencephaly and spina bifida cystica in British Columbia?

How accurate are these empiric risks?

How do they vary with the type of defect involved, the type of birth (livebirth or stillbirth), and important demographic variables such as sex and parity?

Are the risks for these defects different from the risks in other parts of the world?

Are these empiric risk figures different from theoretical risks for these two conditions?
4.1 Frequency of Malformations

**Overall Birth Frequency:** The incidence of anencephaly and spina bifida cystica obtained in this study is shown in Table III. A total of 1063 index cases were ascertained, 466 (43.4%) with anencephaly, and 597 (56.6%) with spina bifida cystica. There were sixteen twin-born cases, and one concordant twin pair. The ratio of males to females was 0.48:1 for anencephaly cases, and 0.87:1 for spina bifida cystica cases, resulting in an overall ratio of males to females of 0.68:1. Stillbirths accounted for 75% of the anencephaly cases and 11% of the spina bifida cystica cases.

According to this study, 1.55 per thousand total births in the province from 1952 to 1970 resulted in either an anencephalic or a spina bifida cystica child. This is similar to incidence figures for British Columbia reported elsewhere (Trimble and Baird, 1977a). The incidence of anencephaly and spina bifida cystica in the province has not changed during the period under study.

**Families:** One thousand and fifty-one index cases in 1028 families linked to the family files. Two hundred and sixty-six of the families had only the single affected birth in the study period, and 762 families had two
Table III

Incidence of Anencephaly and Spina Bifida Cystica in British Columbia

<table>
<thead>
<tr>
<th>Total Births</th>
<th>Anencephaly Number Per Thousand</th>
<th>Spina Bifida Number Per Thousand</th>
<th>Total Abnormal Number Per Thousand</th>
</tr>
</thead>
<tbody>
<tr>
<td>686,326</td>
<td>466 (0.68)</td>
<td>597 (0.87)</td>
<td>1063 (1.55)</td>
</tr>
</tbody>
</table>

\(^1\)From 1952 to 1970; includes livebirths and stillbirths.
or more children. The average family size throughout the study group, counting all births to 1970, was 2.9 births per family. In comparison, the average family size among families with a viable child born in British Columbia in 1952 was 2.5; those families with a viable child born in the province in 1970 were of an average size of 2.2 births per family.

Twelve cases (1.1%) did not link to the family files, and therefore were not included in the estimates of risk - three with spina bifida cystica and nine with anencephaly. Of these twelve cases, ten had surname combinations of Singh-Kaur or Kaur-Kaur, and thus could not be linked. Nine of the ten were female anencephalics; the other was a female with spina bifida cystica. Therefore the birth records of only two cases (0.2%) were not identified by the linkage procedure. One of these was a female with spina bifida cystica without a second surname recorded on the summary record; the other was a male spina bifida cystica case with different double soundex codes on the summary record and the birth index record, due to slight differences in the original soundexing procedures for the summary records and the marriage and birth index records.

4.2 Risks to Sibs

Anencephaly: The risks to sibs of anencephaly index cases are summarized in Table IV. There were 332 anencephaly probands with sibs. Of 396 brothers of anencephalics, one had anencephaly and five had spina bifida cystica. Of 401 sisters, anencephaly was present in nine, and spina bifida cystica was present in seven. Thus 1.5% of brothers and 4.0% of sisters were also affected with a neural-tube closure malformation. The overall risk of both defects was 2.8%, with 1.3% of sibs affected with
Table IV
Risks to Sibs of Anencephaly and Spina Bifida Cystica

<table>
<thead>
<tr>
<th>Index Cases</th>
<th>Total</th>
<th>Brothers % affected</th>
<th>Total</th>
<th>Sisters % affected</th>
<th>Total</th>
<th>All Sibs % affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>147</td>
<td></td>
<td>122</td>
<td>1.6 (0A,2S)</td>
<td>246</td>
<td>1.6 (1A,3S)</td>
</tr>
<tr>
<td>Anencephaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>310</td>
<td>272  1.5 (1A,3S)</td>
<td>279</td>
<td>5.0 (8A,6S)</td>
<td>551</td>
<td>3.3 (9A,9S)</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>457</td>
<td>396  1.5 (1A,5S)</td>
<td>401</td>
<td>4.0 (9A,7S)</td>
<td>797</td>
<td>2.8 (±1.1)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>277</td>
<td>262  3.1 (2A,6S)</td>
<td>238</td>
<td>2.1 (3A,2S)</td>
<td>500</td>
<td>2.6 (5A,8S)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>317</td>
<td>319  0.9 (1A,2S)</td>
<td>290</td>
<td>2.8 (6A,2S)</td>
<td>609</td>
<td>1.8 (7A,4S)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>594</td>
<td>581  1.9 (3A,8S)</td>
<td>528</td>
<td>2.5 (9A,4S)</td>
<td>1109</td>
<td>2.2 (±0.9)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRAND TOTAL</td>
<td>1051</td>
<td>977  1.7 (4A,13S)</td>
<td>929</td>
<td>3.1 (18A,11S)</td>
<td>1906</td>
<td>2.4 (±0.7)</td>
</tr>
</tbody>
</table>

A = anencephaly; S = spina bifida cystica

The 95% confidence limits were calculated according to the formula

\[ p \pm 1.96\sqrt{pq/n} \]

where \( p \) = proportion affected
\( q = 1 - p \)
\( n = \) number of cases
anencephaly, and 1.5% affected with spina bifida cystica. The risks for either defect were not significantly different. There was no significant difference in the proportions of affected sibs of male and female probands (1.6% as compared to 3.3%), nor was there any difference in risk between brothers and sisters of all anencephaly propositi. The sisters of female anencephaly probands did have a significantly higher risk (5.0%) than all other sibs taken together (1.5%).

**Spina Bifida Cystica:** Four hundred and fifty-two spina bifida cystica probands had sibs. The risks to those sibs are also shown in Table IV. Among the 581 male sibs there were eleven affected, or 1.9%; three with anencephaly and eight with spina bifida cystica. Nine of 528 sisters had anencephaly, and four had spina bifida cystica, resulting in an overall risk to female sibs of 2.5%. The combined risk to brothers and sisters of spina bifida cystica propositi was 1.1% for anencephaly and 1.1% for spina bifida cystica, or 2.2% for either defect. The risks to sibs of male and female probands were not significantly different (2.6% as compared to 1.8%). A higher risk was seen in sibs of the same sex of the proband, although these increases were also not significant. For example, the risk to brothers of male probands was 3.1%, as compared to a risk of 2.1% to sisters of male probands. Similarly, the risk to sisters of female probands, 2.8%, was greater than the 0.9% observed among the brothers of affected females.

---

3 The $X^2$ statistic was used throughout this section to investigate agreement between sample proportions, using 2xk contingency tables with k-1 degrees of freedom. Tests were compared to a critical $X^2$ at $p = 0.05$. 

The overall risk of a neural-tube closure malformation to sibs of both anencephaly and spina bifida cystica probands was 2.4%. No difference was seen in the risks to sibs of anencephaly propositi and the sibs of spina bifida cystica propositi. Likewise, there was no difference in risk to sibs of male probands (2.3%) and female probands (2.5%). Although the risk to sisters was greater than that to brothers of propositi (3.1% as compared to 1.7%), again, this increase was not significant. However, there was a significant increase in the proportion of affected female sibs with anencephaly (1.9%) compared to the proportion of affected male sibs with anencephaly (0.4%). The proportion of affected sibs of stillborn probands (2.9%) (Table V) was not appreciably greater than that to sibs of liveborn probands (2.1%).

Therefore, the only significant differences in the risks to sibs of neural-tube closure defects were found when considering the effect of sex on the risk of anencephaly. There was a tendency for female sibs, particularly the sisters of anencephalic probands, to have a higher risk of anencephaly than male sibs. This may be partly due to differential loss of male sibs early in pregnancy. It may also be partly a consequence of the higher proportion of affected females than males in the study population (particularly among the anencephalics), and the fact that the calculation of sibling risks involves the counting of multiply-affected families more than once.

4.3 Recurrence Risks

There were 1073 sibs born after 560 index cases that were the first affected in a family, as shown in Table VI.
Table V

Risks to Sibs of Anencephaly and Spina Bifida Cystica, by Type of Birth of Proband

<table>
<thead>
<tr>
<th>Index Cases</th>
<th>Total</th>
<th>% affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livebirths</td>
<td>1226</td>
<td>2.1 (13A,13S)</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>680</td>
<td>2.9 (9A,11S)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1906</td>
<td>2.4 (22A,24S) (±0.7)</td>
</tr>
</tbody>
</table>

1 95% confidence limits.
Table VI

Recurrence Risks of Anencephaly and Spina Bifida Cystica

<table>
<thead>
<tr>
<th>Index Cases</th>
<th>Total</th>
<th>Brothers % affected</th>
<th>Total</th>
<th>Sisters % affected</th>
<th>Total</th>
<th>All Sibs % affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Anencephaly</td>
<td>147</td>
<td>78  2.6 (0A,2S)</td>
<td>67</td>
<td>0.0 (0A,0S)</td>
<td>145</td>
<td>1.4 (0A,2S)</td>
</tr>
<tr>
<td>Female Anencephaly</td>
<td>310</td>
<td>154 2.6 (1A,3S)</td>
<td>149</td>
<td>2.7 (3A,1S)</td>
<td>303</td>
<td>2.6 (4A,4S)</td>
</tr>
<tr>
<td>Anencephaly TOTAL</td>
<td>457</td>
<td>232 2.6 (1A,5S)</td>
<td>216</td>
<td>1.9 (3A,1S)</td>
<td>448</td>
<td>2.2 (4A,6S)</td>
</tr>
<tr>
<td>Male Spina bifida</td>
<td>277</td>
<td>135 2.2 (0A,3S)</td>
<td>122</td>
<td>0.0 (0A,0S)</td>
<td>257</td>
<td>1.2 (0A,3S)</td>
</tr>
<tr>
<td>Female Spina bifida</td>
<td>317</td>
<td>198 1.5 (1A,2S)</td>
<td>170</td>
<td>3.5 (5A,1S)</td>
<td>368</td>
<td>2.4 (6A,3S)</td>
</tr>
<tr>
<td>Spina bifida TOTAL</td>
<td>594</td>
<td>333 1.8 (1A,5S)</td>
<td>292</td>
<td>2.1 (5A,1S)</td>
<td>625</td>
<td>1.9 (6A,6S)</td>
</tr>
<tr>
<td>GRAND TOTAL</td>
<td>1051</td>
<td>565 2.1 (2A,10S)</td>
<td>508</td>
<td>2.0 (8A,2S)</td>
<td>1073</td>
<td>2.1 (10A,12S)</td>
</tr>
</tbody>
</table>

A = anencephaly; S = spina bifida

195% confidence limits.
Anencephaly: Among 232 younger brothers of anencephaly probands, there were five with spina bifida cystica and one with anencephaly. Out of a total of 216 younger sisters, three had anencephaly and one had spina bifida cystica. Thus the recurrence risk after one affected was 2.6% for males and 1.9% for females, or 2.2% overall, with no difference in the risk of either neural-tube closure defect (0.9% for anencephaly and 1.3% for spina bifida cystica). The risk to subsequent sibs of male anencephalic probands (1.4%) was not significantly changed from that to subsequent sibs of female propositi (2.6%).

The higher risk to sisters of female anencephaly probands was not evident when considering subsequent female sibs only.

Spina Bifida Cystica: The proportion affected of 333 younger brothers of spina bifida cystica was 1.8%; of which one was an anencephalic and five had spina bifida cystica. Of 292 younger sisters, 2.1% were affected, five with anencephaly and one with spina bifida cystica. Thus there was an equal number of younger sibs affected with anencephaly and with spina bifida cystica, the overall risk being 1.9%. There was no significant difference in risk with respect to the sex of the proband (1.2% for males as compared to 2.4% for females). Sisters of female spina bifida cystica propositi had the highest risk (3.5%), while sisters of male spina bifida cystica propositi had the lowest risk (0.0%); however, these differences were also not significant.

The overall recurrence risk after one neural-tube closure malformation was 2.1%, or 22 out of 1073 subsequent sibs. This risk was the same regardless of the sex or the type of malformation of the proband. There was
no tendency for subsequent sibs to have the same type of malformation
the proband, although there was a higher proportion of anencephaly cases
among affected younger sisters of probands than among younger brothers with
neural-tube closure malformations (1.6% as compared to 0.4%); and a higher
proportion of spina bifida cystica cases among younger brothers than among
younger sisters of probands (1.9% as compared to 0.4%). Again, differ­
ential early loss of affected individuals of one sex may account for these
differences. The risk to subsequent sibs of stillborn cases (Table VII)
was the same as the recurrence risk after a liveborn case (2.1% as compared
to 2.0%).

Parity: The risk of recurrence of neural-tube closure defects
was examined by parity of the first index case in Table VIII. Among 255
sibs of firstborn male probands, three, or 1.2%, were also affected with a
neural-tube closure defect. Only one of 94 subsequent sibs of secondborn
male probands, or 1.1%, had a neural-tube closure malformation. Among 428
sibs of primapara female propositi, 2.6%, or fourteen, were also affected
with anencephaly or spina bifida cystica, while 3.1%, or five, of 160 younger
sibs of secondborn female propositi had anencephaly or spina bifida cystica.
The risk to younger sibs of all firstborn probands was 2.0%. The risk to
subsequent sibs of secondborn propositi was 2.4%. There was no difference
in recurrence risk by parity or sex of the first affected case.

Risk after Two Affected: There were 21 families with at least
two sibs with neural-tube closure defects, of which seven had children born
after the second affected case (Table IX). Of twelve subsequent female
Table VII

Recurrence Risks of Anencephaly and Spina Bifida Cystica, by Type of Birth of Proband

<table>
<thead>
<tr>
<th>Index Cases</th>
<th>Total</th>
<th>% affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livebirths</td>
<td>644</td>
<td>688</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>407</td>
<td>385</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1051</td>
<td>1073</td>
</tr>
</tbody>
</table>

\(^1\) 95% confidence limits.
Table VIII
Recurrence Risks of Anencephaly and Spina Bifida Cystica, by Parity of Proband

<table>
<thead>
<tr>
<th>Sibship</th>
<th>Number of Cases</th>
<th>Recurrence Risk after One Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Subsequent Sibs</td>
<td>% Affected</td>
</tr>
<tr>
<td>1 male affected,^1^ para 1</td>
<td>132</td>
<td>255</td>
</tr>
<tr>
<td>1 male affected, para 2</td>
<td>52</td>
<td>94</td>
</tr>
<tr>
<td>1 female affected, para 1</td>
<td>201</td>
<td>428</td>
</tr>
<tr>
<td>1 female affected, para 2</td>
<td>89</td>
<td>160</td>
</tr>
<tr>
<td>1 affected (either sex), para 1</td>
<td>333</td>
<td>683</td>
</tr>
<tr>
<td>1 affected (either sex), para 2</td>
<td>141</td>
<td>254</td>
</tr>
<tr>
<td>OVERALL RISK</td>
<td>1051</td>
<td>1073</td>
</tr>
</tbody>
</table>

^1^affected with either anencephaly or spina bifida cystica.
^2^95% confidence limits.
Table IX
Recurrence Risks of Anencephaly and Spina Bifida Cystica after Two Affected Sibs

<table>
<thead>
<tr>
<th>Index Case</th>
<th>Affected Older Sib</th>
<th>No. of Families</th>
<th>Number of subsequent siblings</th>
<th>% Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M F</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>M F</td>
<td>Number Affected</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 6</td>
<td>0 1</td>
<td>9.1</td>
</tr>
<tr>
<td>anencephaly</td>
<td>spina bifida</td>
<td>3</td>
<td>0 1</td>
<td>9.1</td>
</tr>
<tr>
<td>spina bifida</td>
<td>anencephaly</td>
<td>1</td>
<td>0 0</td>
<td>0.0</td>
</tr>
<tr>
<td>spina bifida</td>
<td>spina bifida</td>
<td>3</td>
<td>0 0</td>
<td>0.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>7</td>
<td>9 12</td>
<td>4.8</td>
</tr>
</tbody>
</table>

195% confidence limits.
children, one was affected with anencephaly. None of the nine younger brothers had a neural-tube closure malformation. The proportion of subsequent children affected, then, was 4.8%. None of the children born after the second affected case had any other central nervous system malformation.

4.4 Other Considerations

Twins: Information on the sixteen twin-born index cases is summarized in Table X. The proportion of twins among the index cases (1.5%) is lower, though not significantly so, than the proportion expected in the general population (Parkes, 1969). One pair of male twins was concordant for anencephaly. In addition, two female twins of anencephaly index cases were reported to have hydrocephaly.

Other CNS Malformations: Among the 1871 sibs of index cases nine had other central nervous system malformations. These included one with microcephaly, one with congenital absence of the nucleus of a facial nerve, and seven with congenital hydrocephaly without spina bifida cystica. The proportion of cases of hydrocephaly does not differ significantly from the British Columbia population frequency (1.04 per 1000 births).

\[4\text{The proportion of twin births in most Western countries is from one in 80 to one in 100 births, implying that, in the general population, one person in 45 is a twin.}\]
Table X
Twin-born Index Cases of Anencephaly and Spina Bifida Cystica

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Total Pairs</th>
<th>Sex of Twin Pairs</th>
<th>Concordant Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MF</td>
<td>FM</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Spina Bifida</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

¹Sex of affected twin listed first.

²Two FF twin pairs had a second twin with hydrocephaly.
5.1 Ascertainment

Both anencephaly and spina bifida cystica are easily recognizable at birth. Anencephaly is a lethal condition and about 90% of cases are documented on mortality records (Elwood, J.M., 1976a). A smaller proportion, at most about 70%, of cases of spina bifida cystica are also found on mortality records (Elwood, J.M., 1976a). Hospital records are not a reliable source of ascertainment of spina bifida cystica patients since the diagnosis of malformation is not always clear (Lorber, 1961). Therefore, in order to ascertain most of the cases of these neural-tube closure defects occurring in a population, a comprehensive search must be made of several types of records of mortality and morbidity.

Previous family studies of neural-tube closure malformations have utilized various combinations of available records to ascertain cases. The best ascertainment has been achieved in London and in Liverpool, where death and stillbirth records, registry records, and (in London) hospital records were searched. The London series reported approximately 95% ascertainment; other recent studies reported proportions lower than this.
The British Columbia study utilizes several types of records of mortality and morbidity in identification of index cases, including vital records of death, stillbirth, and livebirth, and register records. The process of ascertainment by means of computerized pooled records is an excellent one for conditions such as anencephaly or spina bifida cystica that are easily recognized and diagnosed, and that are routinely documented on population-based records. The scanning of these types of documents for the whole of the British Columbia birth population from 1952 to 1970 has resulted in truncate selection of cases; consequently biases due to the nonrepresentativeness of the sample or small sample size are avoided. Because ascertainment is on an individual basis, the probability of identifying an index case is independent of the size of the family or the number of affected sibs. The use of population-based records ensures also that there are no missing individuals in a pedigree. Therefore ascertainment biases do not arise. The computerization of these records makes possible the analysis of the large amounts of data that are generated in a survey of this size. Because of the nature of the records searched, and the procedures used in the identification process, ascertainment of British Columbia-born cases of anencephaly and spina bifida cystica between 1952 and 1970 is considered to be greater than 95% complete.

Errors in this method of ascertainment arise when instances of neural-tube closure defects are not recorded on the appropriate documents, or when malformations are incorrectly coded. Furthermore, only information noted on the original records is available to the researcher; because of the confidential nature of these documents, it is difficult if not impossible to go back to the index case or the family of the index case in order to confirm a diagnosis or to retrieve additional information. In this study, there
may be cases included in which encephalocele has been misdiagnosed as anencephaly. In addition, there may be instances where the aetiology of the neural-tube closure defect is known to be other than multifactorial (Holmes, 1976). For example, meningomyelocele is known to be associated with chromosomal anomalies and with certain teratogens. However, the relative rarity of these errors and the low familial risk associated with these alternative aetiologies means that these errors should not appreciably affect the results of the study.

This method is less useful for conditions that are not easily recognized or that constitute a problem in diagnosis. Other conditions for which ascertainment by means of pooled records is less effective include those that are not routinely recorded on vital records or other population-based health documents.

A large source of error among previous family studies of anencephaly and spina bifida cystica has been the loss of family information. From 18% (Carter and Evans, 1973) to 47% (Smithells et al., 1968) of families of index cases have been lost to follow-up because of difficulties in tracing families, non-co-operation, or illegitimacy. Unfortunately, it is very difficult to assess the degree of bias introduced in this manner. In contrast, a search of the family groupings of British Columbia birth and marriage records retrieved all but 1.1% of the families of the index cases. These family groupings are particularly useful for genetic studies. They are currently being extended, through the British Columbia Record Linkage Project, to include second-degree relatives, so that more extensive family analyses can be carried out in the future.
The family files used in the study did not include records of births that occurred outside the province of British Columbia, nor did they include records of births before 1952 or after 1970. However, neither of these omissions should bias the results of the study since there is no reason to suppose that the sibling risk for those missed births is any different from that among the observed births. Therefore the results obtained from this study can be considered representative of the risks in the population of British Columbia during the years 1952 to 1970.

5.2 Empiric Sibling Risks

The risk of neural-tube closure malformations among sibs of children affected with either anencephaly or spina bifida cystica in British Columbia is lower than that reported in any other locality. Furthermore, this risk does not change according to the type of malformation, the type of birth, or the sex of the proband, or by the sex of the sibs.

Other studies of familial risks of anencephaly and spina bifida cystica have been conducted among largely Caucasian populations. Most of these studies have taken place in the British Isles. The risk among sibs of neural-tube closure defects in Great Britain varies from 3.9% (Smithells et al., 1968) to 5.6% (Williamson, 1965; Richards et al., 1972). About 60% of the population of British Columbia came originally from the British Isles, and 25% from Western Europe; yet the risk in British Columbia families is only 2.4%, or approximately one-half of the risk in Great Britain. The risk to sibs in British Columbia is also lower than the two North American studies reported: 3.2% in New York (Milham, 1962) and 4.6% in Rhode Island (Yen and MacMahon, 1968). These large differences in risk between populations of
essentially the same genetic background suggest that environmental factors may be largely responsible for the low risks in North America as compared to Great Britain, and in particular the extremely low risk in British Columbia. In fact, these differences may be even greater than the above-mentioned studies indicate. The calculation of the proportion of sibs affected in surveys previous to the British Columbia study has been carried out on the basis of single ascertainment; that is, on the assumption of just one proband per family. Since ascertainment was not considered to be complete in any of these studies, this procedure underestimated the true sibling risk. Therefore other areas may have an even higher risk among sibs than has been reported.

No consistent changes were observed when examining the differences in risk to sibs of neural-tube closure defects by various factors that influence the population incidence of ASB. However, certain trends observed in the data were consistent with those in other studies, particularly the family study in London (Carter and Evans, 1973).

The London study is of particular interest since it was conducted in a relatively low-incidence area of the British Isles, and it examined several of the same variables that were considered in the British Columbia study. A comparison of the population incidence and the proportion of sibs affected in the two areas is shown in Table XI. Both studies observed fewer affected brothers of probands than sisters. The sibs of anencephaly index cases were more often affected, in both London and British Columbia, than the sibs of spina bifida cystica propositi. In London, there were fewer affected sibs of male anencephaly cases than female anencephaly cases; no difference was seen among spina bifida cystica probands. The risk to sibs of male anencephalics was also higher than the sibling risk of female
<table>
<thead>
<tr>
<th>Area</th>
<th>Malformation</th>
<th>Incidence in Population (per thousand births)</th>
<th>Incidence among Sibs (%)</th>
<th>Recurrence Risk (%)</th>
<th>Relative Proportion Sibs/Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.C.</td>
<td>anencephaly</td>
<td>0.68</td>
<td>2.76(\pm 2.41 \pm 0.69^2)</td>
<td>2.23(\pm 2.05)</td>
<td>40.6(\pm 15.5)</td>
</tr>
<tr>
<td></td>
<td>spina bifida</td>
<td>0.87</td>
<td>2.16</td>
<td>1.92</td>
<td>24.8(\pm 15.1)</td>
</tr>
<tr>
<td>London</td>
<td>anencephaly</td>
<td>1.54</td>
<td>5.44(\pm 4.45 \pm 1.05)</td>
<td>4.17(\pm 4.61)</td>
<td>35.3(\pm 15.1)</td>
</tr>
<tr>
<td></td>
<td>spina bifida</td>
<td>1.41</td>
<td>3.42(\pm 5.17)</td>
<td>1.67</td>
<td>24.3(\pm 15.1)</td>
</tr>
</tbody>
</table>

\(^1\) Carter and Evans 1973

\(^2\) 95% confidence limits.
anencephaly cases in British Columbia; however, the reverse trend was evident among spina bifida cystica index cases. In both London and British Columbia, the highest risk was for female sibs of female anencephaly index cases. However, none of these differences were significant in either study, except for the last mentioned, and, in both studies, there is no real indication that there is a difference in the proportion of sibs affected according to the malformation of the index case.

In London, the risk for subsequent sibs of anencephaly probands was lower than for all sibs (4.17% of younger sibs; 5.44% of all sibs); the risk for later-born sibs of spina bifida cystica index cases was higher than the risk to all sibs (5.17% of younger sibs; 3.42% of all sibs). For the London study, the risk to all sibs was calculated counting each family only once, considering the first ascertained case in each family as the index case. The recurrence risk among younger sibs of both type of probands in the British Columbia study was lower than the corresponding risk to all sibs, since the calculation of the risk to all sibs involved accounting for multiply-affected families more than once. Therefore, the differences between the risk to all sibs and the recurrence risk in the two studies are probably due to differences in the methods of calculating risk. The risk to sibs and risk of recurrence after one affected sib were not appreciably different from one another in either study. Several other studies (Williamson, 1965; Carter et al., 1968; Smithells et al., 1968; Richards et al., 1972; Carter and Evans, 1973) have reported a tendency for sibs of an affected individual to have the same type of malformation as the index case; this tendency was not observed in the British Columbia study.
The results of this study and other family studies of neural-tube closure defects indicate that the risk of a neural-tube closure malformation among sibs of affected individuals is not markedly influenced by factors such as the sex, type of malformation, type of birth, or parity of the proband, at least for the population studied. Certain consistent trends in the data from both London and British Columbia do suggest, however, that these factors may influence the risk to sibs of neural-tube closure defects, but that studies so far have been too small to detect this influence.

The risk of recurrence after two affected in a sibship has been estimated as 12% in one English study (Carter and Roberts, 1967), or about twice the risk after one affected child. Although the amount of data for British Columbia is small, the calculated risk of 4.8% suggests that the recurrence risk after two affected is also lower in British Columbia than in England. If one assumes that the risk after two children with ASB is double the risk after one affected case, the recurrence risk after two affected would be 4.2% in British Columbia - appreciably lower than the risk in the south of England.

5.3 Theoretical Sibling Risks

The findings of the present study, like those of previous studies on ASB, are suggestive of a multifactorial aetiology for neural-tube closure defects, depending on both a genetic predisposition to these conditions, and environmental influences.

As mentioned previously, the increased frequency of these conditions among relatives of affected individuals, and the variation in incidence among different ethnic groups (in particular the extremely low incidence
among blacks in all parts of the world) are strong indications of a genetic influence in the causation of these defects. Another test of the degree of genetic influence in the aetiology of these malformations is the estimate of heritability. The heritability estimates, using Falconer's method, are 61%, 58%, 66%, and 68%, for the British Columbia, South Wales, Glasgow, and London series, respectively. These proportions have been used as minimum estimates of the degree of genetic determination. However, since the heritability is derived from the correlation between relatives, it inevitably includes the influence of common family environment as well as genetic causes of resemblance between relatives. Therefore, although these figures are suggestive of genetic factors, the degree of genetic determination cannot be accurately assessed using this method. The similarity among these estimates does imply, however, that the combined influence of genetic factors and common family environment does not vary a great deal in these different areas. Therefore the variation in population incidence and sibling risks must be due to other factors.

The data in this study demonstrate a risk of neural-tube closure defects to sibs of affected individuals greater than that for the general population; a further increase in risk after two affected individuals in a family; and a lower sibling risk compared to the sib risk in an area of higher population incidence. All these results are compatible with a polygenic mode of inheritance of neural-tube closure defects. A strictly

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The formula for calculating the heritability is:

\[ h^2 = 2 \left( \frac{x_g - x_r}{a} \right) \]

where 

- \( x_g \) = deviation of threshold from mean in general population
- \( x_r \) = deviation of threshold from mean in relatives
- \( a \) = mean deviation of affected individuals from the population mean (Falconer, 1965).
environmental model would also account for all these findings, but seems less plausible when considering the above-mentioned evidence of genetic influence in the development of these anomalies. The information on twins in this study is also not incompatible with a polygenic hypothesis.

One area of disagreement between the polygenic model and the British Columbia data is in estimation of sibling risk. The theoretical overall risk to sibs of children with anencephaly and spina bifida cystica is approximately the square root of the population incidence in British Columbia, or 3.9%. This figure is higher than the empiric risk; therefore the actual risk is less than would be expected from genetic considerations alone. However, there is a significant error factor in this theoretical risk.

The model also predicts that the lower the population incidence, the higher the relative risk to sibs. As indicated in Table XI, this does hold true in a comparison between London and British Columbia rates, although comparisons with areas of extremely high (Williamson, 1965; Richards et al., 1972) or extremely low (Smithells et al., 1968) incidences do show a greater difference.

Certainly the hypothesis of polygenic inheritance cannot account for all the variation observed in liability to these conditions, and it does not lead to an accurate estimate of the risk to sibs, although it does furnish an adequate explanation of the genetic factors involved. Therefore environmental factors must continue to be taken into account when studying the causation of these defects. Furthermore, in order to determine the extent of genetic influence in the aetiology of these defects, more information on twins, half-siblings, and second-degree relatives is needed.
Since the risk of neural-tube closure defects to sibs of affected individuals cannot be predicted by either genetic or environmental factors alone, the best possible estimates of risk come from empiric information. Therefore, the data from this study give the best possible estimates of sibling risk in British Columbia at this time. Strictly speaking, the figures derived in this study are applicable only to the population from which they were derived, that is, the population of British Columbia births from 1952 to 1970. However, the fact that the population incidence in the province has not changed during the period under study is a fairly good indication that the factors that influence the causation of neural-tube defects in this province are relatively constant over time, and that the risks calculated from this data are relevant also to the present population.

There is a possibility that the population incidence and sibling risk are higher in some ethnic groups (e.g. Irish, Sikhs) residing in British Columbia, and lower in others (e.g. Orientals). Although the present study was not able to determine this due to insufficient data, it perhaps should be considered in genetic counselling situations. Further studies are needed to establish the risks for these groups.

The results of the present survey have particular implications for the British Columbia amniocentesis programme. At present about 3.8% of cases of anencephaly and spina bifida cystica born in this province are familial. The proportion of recurrent cases is about half that estimated from other data, yet it is still much higher than the risk of a Down Syndrome child, for example, to a woman aged 38 (0.31%) (Trimble and Baird, 1977b), for whom amniocentesis is routinely offered. Therefore a continuation of the screening of pregnancies subsequent to the birth of a child with a neural-tube closure defect seems worthwhile.
Empiric risks of anencephaly, spina bifida cystica, and other central nervous system malformations were determined for the sibs of children affected with anencephaly or spina bifida cystica born in British Columbia. The risk to sibs of either anencephaly or spina bifida cystica was found to be 2.4%, about fifteen times the population incidence in British Columbia. The risk to subsequent sibs of the first affected individual in a family was not significantly different from the risk to all sibs. Subdividing the data by sex, type of malformation, parity, or type of birth of the proband showed no appreciable differences in risk. Brothers and sisters of propositi had the same risk of a neural-tube closure defect; and there were equal proportions of cases of anencephaly and spina bifida cystica among sibs. The risk of recurrence of anencephaly or spina bifida cystica after two previously affected sibs was 4.8%, or approximately double the risk after one affected sib. No increased risk of any other central nervous system defect was observed in the families of the index cases.

The sibling risks of anencephaly and spina bifida cystica in British Columbia are much lower than that reported elsewhere. They are approximately one-half the sibling risks in Great Britain. They are also
the lowest reported in North America. Comparison of the results of this study with other family studies of ASB indicate that geographical differences in risk can be attributed largely to environmental factors in causation. A tendency towards a higher risk among sibs of anencephaly cases, and among sisters of all index cases, was observed in British Columbia and in London, suggesting that these factors may influence the sibling risks of anencephaly and spina bifida cystica to some degree.

The observed sibling risks of these conditions were less than that predicted by one model of polygenic inheritance with a threshold effect. The degree of genetic determination of these defects in British Columbia was estimated to be about 60%.

The technique used in this study, of utilizing the linked family records available in British Columbia to assess sibling risks, has proved useful in justifying the continuation of amniocentesis service to mothers of children with anencephaly or spina bifida cystica. This technique can be extended to study the sibling risks of other congenital malformations in the province, in particular those with a higher frequency or those that present greater medical problems to the community.


