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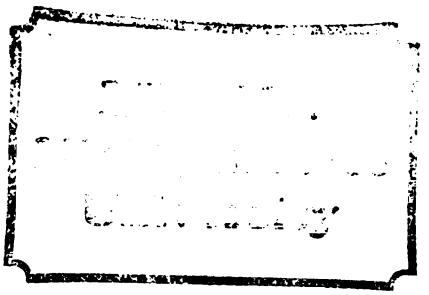

This is to certify that the

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AMONG NEURAL TUBE DEFECTS

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HELGA VALDMANIS TORIELLO

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INVESTIGATION OF HETEROGENEITY AMONG NEURAL TUBE DEFECTS

By

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ABSTRACT

INVESTIGATION OF HETEROGENEITY
AMONG NEURAL TUBE DEFECTS

By

Helga Valdmanis Toriello

The goal of this study was to determine whether heterogeneity exists among the neural tube defects (NTD). Families of children with NTD were sent questionnaires which asked about pregnancy history, family history, and other background information (such as blood types and ethnic origin). The index population was subdivided by defect location. These subgroups consisted of index patients with thoraco-lumbo-sacral defects (T group), lumbo-sacral defects (L group), sacral defects (S group), encephaloceles (E group), and other defects, including isolated thoracic, cervical, and thoraco-lumbar defects (O group). These subgroups were compared to each other to determine whether heterogeneity exists (intra-group comparisons). Comparisons were also made between index patients and a control group and index patients and their normal siblings (inter-group comparisons). Since no differences were found between the L and S groups and the O and E groups, they were pooled into two groups.

Significant intra-group differences included a greater incidence of miscarriage in T and OE sibships as compared

to the LS group, and a shorter inter-pregnancy gap in the OE group as compared to the OE group, and a greater incidence of anti-emetic usage, maternal hormone usage, and conception following an abotion in the OE group as compared to the LS group. A number of significant inter-group differences were found as well. These included a greater incidence of febrile illness and anti-emetic usage in the T group, a greater incidence of febrile illness and blood type B and a lower incidence of blood type A and pyloric stenosis in relatives in the LS group and a greater incidence of abortions in the sibship, anti-emetic and hormone usage, gynecological problems, shortened inter-pregnancy gap, and conception following an abortion in the OE group.

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INTRODUCTION AND LITERATURE REVIEW

Many investigations of the embryology, causes, and distribution of neural tube defects (NTD) have been done. Most studies have examined anencephaly, iniencephaly, spina bifida and encephalocele as a homogeneous group of NTD. Since data exist which suggest that more than one embryological error can lead to a NTD, it is possible that genetic heterogeneity exists among the NTD based on these different pathogeneses. As a result, studies which pooled all NTD could miss factors significant for only certain NTD. One possible way of testing whether heterogeneity exists is by separating the NTD into groups as homogeneous as possible and then comparing each group to the others in an attempt to detect genetic or environmental differences. NTD can be categorized by the location of the defect. Therefore this thesis examined whether significant differences exist between the various NTD when separated by the location of the defect.

Selected parameters were chosen for examination based on previous findings by other authors. The purpose of the literature review is to illustrate both the reason for choosing certain parameters, and the disagreement among authors regarding the causes of NTD.

DEVELOPMENT OF THE NEURAL TUBE

In the normal sequence of development, the first step is the formation of the neural plate, which occurs on the 18th day. The neural tube closure begins on the 21st day. The inducers for closure are the parachordal mesoderm (somites and precursors of somites).[1]

Histologically, closure is the result of differential contraction at the apical and basal surfaces of the neural plate cell. Beneath the apical surface of these cells, there exists a thin band of 40-50 Å microfilaments oriented parallel to the surface and annularly about the neck of each cell. These filaments have been compared, structurally and functionally, to actin by Linville *et al.* in 1972.[2] The closure of the neural plate starts in the cervical region at the level of the fourth through seventh somites. Anterior closure is completed on the 26th day, and posterior closure is completed on the 28th day of development. The last point of closure is at the level of the 25th somite, which in turn corresponds to the level of the L-1, L-2 vertebral interspace. At twelve weeks gestation, the neuromeres correspond anatomically to vertebral segments.[3] However, since the growth of the neural tube slows in the 4th month, whereas that of the vertebral canal continues at the same rate, the spinal cord ends at L-1/L-2 and the roots of the nerves are pulled down to form the cauda equina below the spinal cord.

Meanwhile, the neural tube induces formation of the posterior arches of the vertebrae and the cranial vault. The part of the somite which will become the vertebral column is the sclerotome. In the 6th week of gestation, 6 centers of chondrification appear. Two centers are lateral to the notochord (and will incorporate the notochord to become the centrum), two are lateral to the neural tube (and will become the neural arch and spinous process), and two are at the union of the arch and centrum and will become the transverse processes.[4]

In the ninth week, ossification begins by the invasion of pericostal vessels into the centrum. The ossification centers for the centra appear first in the lower thoracic and upper lumbar regions, and develop more rapidly caudally than cranially. Fusion of the lumbar neural arches is completed between the 1st and 7th year, whereas the sacral arches fuse even later.[4]

DESCRIPTION OF DEFECTS

The term neural tube defects (NTD) refers to a constellation of birth defects affecting the brain and spinal cord. Included in this category are: (1) anencephaly, (2) iniencephaly, (3) encephalocele, (4) myelomeningocele, and (5) meningocele, but not isolated hydrocephalus.

Defects in Brain and Skull

Anencephaly is the partial or total absence of the brain. The pituitary gland is absent and therefore the adrenal glands are hypoplastic. The calvaria does not develop, and the frontal, parietal, and occipital bones are partially missing. In 50% of the cases, rachischisis of the cranium and vertebrae is present.

When the posterior portion of the skull fails to fuse, the abnormality is called cranium bifidum. If the meninges, or brain and meninges herniate through this defect, an encephalocele results. This protrusion is usually covered by skin, and occurs most often in the occipital region.[5]

Ininencephaly is a developmental defect characterized by absence of laminar and spinal processes of cervical, thoracic, and occasionally lumbar vertebrae, with a reduction in numbers and irregular fusion of these vertebrae. The brain and much of the cord often occupy a single cavity.

Defects of Spinal Cord and Vertebrae

Spina bifida is a failure of vertebral arch fusion and is of two types. When it is not evident externally, it is called spina bifida occulta (SBO). When it is accompanied by a herniation of cord or meninges, it is called spina bifida cystica (SBC). SBC which has meningeal herniation containing spinal nerve roots is myelomeningocele. A meningocele, on the other hand, does not involve the spinal cord

or nerve roots.[4]

Types of spina bifidas which are seen include lumbosacral, cervical, upper thoracic, cervical with upper thoracic, and anencephaly with cervical. There are also certain vertebral defects which are not seen. These include localized thoraco-lumbar, total thoracic, and total cervical and thoracic spina bifidas.[6]

Epstein[7] noted that 86% of cases of SBC are lumbosacral, 9.5% cervical, and 4.5% thoracic. In a series of 1390 patients, Matson[8] had found that 78% were lumbosacral, 10% thoraco-lumbar, 4% cervical and 7% thoracic.

Other spinal cord defects also exist. These include diastematomyelia, in which the cord is duplicated, syringomyelia, in which there is random single or multiple cavity formation with the cord, and hydromyelia, in which the spinal cord's central canal is dilated.

Defects associated with, but not affecting the cord are lipoma, a superficial mass of fat which often extends to the spinal canal, and dermal sinus, which is any stratified squamous epithelium-lined depression or tract extending inward from the skin surface.[9] When this tract is superficial to the sacral fascia and contains hairs, it is called a pilonidal sinus. When it extends deeper and communicates with the dura, it is called a dermal cyst. This defect may be found anywhere along the spinal cord, but is usually found in the fifth lumbar region.[9]

THEORIES OF PATHOGENESIS

Several theories have been proposed to account for both the causes of anencephaly and the associations between anencephaly and other congenital abnormalities. Perhaps the simplest and most popular theory proposed to explain anencephaly is the theory of neural tube non-closure put forth by Von Recklinghausen in 1886.[10] In this hypothesis, failure of anterior neuropore closure results in failure of induction of surrounding tissues, with the result being the clinical picture seen in anencephaly.

However, Gardner[11] proposed that anencephaly results from neural tube rupture after closure with the cranial defects resulting from an over-distension of the primitive brain. This leads to a disruption of the cranial sclerotome and resultant cranial anomalies. The continuum these anomalies form is craniolacuna, cranium bifidum with encephalocele, cranium bifidum apertum with excencephalus, and anencephalus.

A third major hypothesis is that of Patten,[12] who has demonstrated that neural tube overgrowth (an excess proliferation of cells) rather than "arrest of development" is likely to be the cause of anencephaly. He has shown that, in human anencephalics, plication of the neural tissue exists, and this plication is the result of the neural tube's overgrowth. Plication has also been observed in

animal specimens with experimentally induced neural tube defects.

Vogel and McClenahan[13] proposed another theory to account for anencephaly. In fourteen cases, they have demonstrated abnormalities of cerebral arteries. This raised the question of whether the arterial anomalies were the cause of the cerebral malformations, or caused by them. To answer that question, they cauterized arteries in 6 day old chick embryos and found that 5-7 days later, all the chicks showed arrested cerebral development. Control chicks were cauterized in other regions of the body. These chicks' brains were normal in development. This led to the hypothesis that abnormalities in the vasculature, not neural tube non-closure, lead to anencephaly.

Theories which have been proposed to account for encephaloceles include the neural tube non-closure theory (Von Recklinghausen) and the neural tube rupture theory (Gardner).

However, Caviness et al.[14] described an infant with an occipital encephalocele in which the defect appeared to be secondary to hydrocephalus. They felt that neural tube non-closure could not be responsible because the defect did not correspond to the closure line of the neural tube.

Leong et al.[15] proposed that occipital encephaloceles result from "breaks" in tissue overlying the mesencephalon, with resultant migration of brain tissue into a hernia sac.

They felt that simple non-closure of the anterior neural tube was untenable as a hypothesis, since they had observed well-developed cerebrum and cerebellum in infants affected with encephaloceles. At 4 weeks, there is normally little cerebrum or cerebellum, and it would not be expected to develop if non-closure occurred.

The theories of Von Recklinghausen and Gardner have also been given as explanations for the pathogenesis of SBC. According to Von Recklinghausen, failure of the posterior neuropore closure results in SBC. However, Gardner[16] noted that failure of neural tube closure should not lead to herniation of the meninges. Therefore, he proposed that rupture of the spinal cord after neural tube closure is the cause of neural tube defects. He felt that a progressive distension of the lumen of the entire neural tube is an essential part of the normal embryonic development but that this phase of development occurs after the neural tube is closed. This distension of the cord is caused by an accumulation of embryonic cerebrospinal fluid, which eventually permeates the subarachnoid space.

A dysraphic condition, therefore, represents a morphological continuum based on varying degrees of distension at varying times in the developmental sequence. In order of severity, these dysraphias are: asymptomatic hydromyelia, syringomyelia, external hydromyelia with or without meningocele, diastematomyelia, myelocele, and finally,

posterior gut fistula (external rupture of both roof and floor plates). Gardner cites as evidence for the rupture theory the observation that in some newborns there exists a progression caudally of hydromyelia to diastematomyelia to myelocele. He feels that neural tube non-closure is insufficient to explain this phenomenon.

Accompanying bony abnormalities could be caused by over-distension of the neural tube. Supposedly, when the neural tube over-expands, the transverse plane is moved laterally with consequent shortening of the longitudinal axis. The first tissue which is affected is the sclerotomes. It has been found that the diameter of the developing spinal canal is determined by the diameter of the nervous tissue it encloses. These sclerotomes trophically maintain a certain prescribed distance from the neural tissue. If the gap is too wide for closure to occur, then the newly developed vertebrae may fail to fuse not only posteriorly but anteriorly as well.

Although failure of neural tube closure in chicks has been produced by teratogens (Kalter and Warkany,[17] and Marin-Padilla and Ferm[18]), Gardner feels that this has not been shown to be the case in humans, citing as evidence the lack of cases in which both anencephaly and lumbosacral spina bifida both occur.

McCredie[19] proposed that injury to neural crest cells could cause congenital malformations by having a

theoretical trophic quality disrupted. This trophic effect would possibly affect midline, cylindrical, or solid organs; and if disrupted, a number of defects would result. These defects include limb anomalies, cleft palate, anal stenosis, coarctation of the aorta, microphthalmia, anophthalmos, coloboma, agenesis or hypoplasia of the kidney, liver or spleen, and spina bifida. Evidence cited by McCredie in favor of this theory includes the constant histological finding of sensory ganglion cells within fibrous bands which appear to be tethering the posterior spinal cord to bony defects in spinous processes. This was discovered in surgically explored cases of spinal dysraphism. It appears these bands are damaged sensory nerves, whose injury had led to prevention of complete fusion of the neural arch, with either spina bifida, meningocele, or myelomeningocele being secondary to neural crest damage.

Sever's[20] data supported the theory of neural crest damage. He described a family in which one child had myelomeningocele, an elder sister had coloboma of the left eye, and a younger sibling had bilateral, congenital anophthalmia, presumably due to abortive globe formation. No other family members had birth defects, nor was the mother exposed to any known teratogens. Sever hypothesized that this family represented a case of familial neural crest cell abnormalities, with the defects representing differences in embryonal genotypes and

intrauterine environments.

Therefore, there exist a number of theories which attempt to explain the altered developmental mechanisms responsible for neural tube defects. If more than one mechanism were responsible for neural tube defects, then heterogeneity would be expected to exist for NTD.

RELATED DEFECTS

In addition to the defects of the vertebral column, other defects are frequently associated with NTD.

David *et al.*[21] examined the frequency of other defects found with anencephaly, and noted that urinary tract defects were most common, with a frequency of 19%. Cardiovascular and GI systems were affected in 8%, and genital, skeletal and other defects were also noted. The most common single defects were hydronephrosis (8%), and cleft palate (8%), followed by diaphragmatic hernia (5%), exomphalos (5%), cleft lip (4%), and horseshoe kidney (4%).

Among defects associated with encephalocele, hydrocephalus is most common. Other anomalies such as cleft palate, clubfoot, heart defects and congenital hip dislocation have also been reported (Lorber[22]). Clubfoot and hydrocephalus are also found associated with SBC. Clubfoot occurs when the cauda equina is damaged by the NTD, resulting in muscular denervation in utero, and ultimately joint

deformities affecting the lower limbs.

Hydrocephalus associated with SBC is caused by the Arnold-Chiari malformation, which is a dislocation of part of the brain into the cervical spina canal. The type of defect is almost always a type two Arnold-Chiari malformation, in which there is a tethering effect on the spinal cord caused by spina bifida cystica, which, in addition to the adhesions of the cerebellum and posterolateral portion of the brainstem, serves to displace the brain as far as the fourth ventricle into the spinal canal down to the fifth cervical vertebra. The Arnold-Chiari malformation complicates between 60-90% of cases of myelomeningocele.[23]

Although it has been generally accepted that tethering of the cord in the lumbo-sacral area is the cause of hydrocephalus, there have been some findings which contradict that theory. Cervical spinal nerves have a caudad course when the Arnold-Chiari malformation is present, which support the tethering theory; however, Barry et al.[24] discovered that in the thoracic area, the course of the nerves is essentially normal, which contradicts that theory. Furthermore, hydrocephalus is comparatively rare in sacral spina bifida cystica. A ten week old fetus has been observed with myelomeningocele and the Arnold-Chiari malformation at which time the differential growth of the spinal cord and vertebral column has not begun.[25]

McLennan[26] examined the rib defects in 20 patients with lumbo-sacral myelodysplasia and found bifid, hypoplastic, fused, deformed, abnormally spaced or missing ribs. In 19 out of 20 patients, the abnormal ribs were contiguous, and in 10 out of 20, there were also abnormal thoracic vertebrae, although the rib and vertebral number did not always coincide. The authors concluded that defects of the ribs and lumbo-sacral vertebrae are coincidental, and that they are the result of a teratogen acting in a single period as opposed to the rib defects being secondary to the vertebral defects.

In a larger study of 434 patients with SBC, Van Went et al.[27] noted that the average number of associated defects, both skeletal and non-skeletal, was 2.08 for male patients and 2.33 for female patients. More than 82% of their patients had one or more associated anomalies. Among patients without any additional malformations, a greater proportion were male. However, the only significant finding was that females had a greater incidence of skeletal anomalies than did males ($p < .001$).

Other research on NTD has focussed on the epidemiological data, in an attempt to identify causes of NTD. Data gathered in one locale may show significance, but invariably, data gathered in other locales contradict it.

SEASONAL VARIATION

Seasonal variation in the incidence of NTD is an important indicator that environmental factors play a role in the cause of NTD. Differences are frequently found between locales, as well as between the peaks of anencephaly and spina bifida within the same locale.

Carter[28] noted a low incidence of spina bifida cystica births occurring in May through July, whereas the anencephaly low occurred in March through May, two months earlier. Carter explains this discrepancy by stating that the gestations of anencephalic fetuses tend to be only seven months as opposed to the normal nine. However, the peak in anencephalic births (Dec.-Feb.) occurred one month later than the spina bifida births' peak (Nov.-Jan.). Therefore, the anencephalic conceptions had to have occurred three months later than conceptions of spina bifida affected infants if Carter's contention is correct. This would mean that different events may have caused the peaks in spina bifida births than caused the peak in anencephaly births . Usually, anencephalics are postmature, unless the pregnancy is complicated by hydramnios.[29] Therefore, in a particular season, the times of conception could vary from 30 to 45 weeks prior to the birth.

In Belfast, Elwood et al.[30] found that for the time period of 1956-60, the spina bifida incidence was higher

from January-June, whereas from July-December, the anencephaly incidence was higher.

In other studies (Williamson,[31] Silberg et al.[32] Czeizel et al.[33]), one type of defect showed seasonal variation whereas the other types did not. In Williamson's study, anencephaly had a peak incidence in January-March. Czeizel et al. and Silberg et al. each noted a significant seasonal variation for spina bifida births, but not for encephalocele or anencephaly. All other studies included encephaloceles with spina bifidas.

In summary, there seem to be indications from the studies that anencephaly and spina bifida, and where examined separately, encephalocele and spina bifida have different seasonal patterns, indicating that there could be heterogeneity between these defects. See Table 1 for a summary of the data.

SEX RATIO

Data has also been gathered regarding the sex ratio, which usually significantly differs from unity. Almost all studies agree that the majority of anencephaly and spina bifida affected individuals are females [28,31,33,37,38,42] (see Table 2). However, in a study which examined encephalocele separately from spina bifida, it was found that the

TABLE 1
SEASONAL VARIATION IN THE INCIDENCE OF NTD

Defect	Maximum Incidence	Minimum Incidence	Locale	Divisions used	Significance	References
ASB*	July-Dec.	-	Wales	seasonally	-	34
Anen.	Jan.-Mar.	-	England	seasonally	-	31
SB	-	-	England	seasonally	-	31
Anen.	-	-	Hungary	monthly	-	33
SB	Feb.-Apr.	July-Sept.	Hungary	monthly	$p < .001$	33
Enceph.	-	-	Hungary	monthly	-	33
Anen.	July-Sept.	Apr.-June	Belfast	seasonally	-	30
SB	Jan.-Mar.	Oct.-Dec.	Belfast	seasonally	-	30
ASB	Jan.-Mar.	-	S. Africa	monthly	-	35
SB	May-June	Mar.-Apr.	Nigeria	monthly	-	36
ASB	-	-	New York	-	-	37
Anen.	Dec.-Feb.	Apr.-June	England	monthly	-	28
SB	Nov.-Jan.	June-Aug.	England	monthly	-	28
ASB	-	-	Israel	seasonally	-	38
Anen.	July-Sept.	Jan.-Mar.	Missouri	monthly	-	32
SB	Oct.-Dec.	Apr.-June	Missouri	monthly	$p < .10$	32
Enceph.	Oct.-Dec.	Apr.-June	Missouri	monthly	-	32
SB	-	-	England	semi-annually	-	39
Anen.	Nov.-Jan.	-	Sweden	monthly	$p < .001$	40
SB	Apr.-Sept.	-	Sweden	monthly	$p < .01$	40
Anen.	Jan.-Mar.	July-Sept.	Maritimes-Can.	seasonally	-	41
Anen.	Jan.-Mar.	Apr.-June	Quebec	seasonally	$p < .005$	41
Anen.	Jan.-Mar.	Apr.-June	Ontario	seasonally	-	41
Anen.	Oct.-Dec.	Apr.-June	Prairies-Can.	seasonally	$p < .05$	41
Anen.	Oct.-Dec.	July-Sept.	Brit. Columbia	seasonally	-	41

*ASB - Anencephaly and Spina Bifida

TABLE 2

SEX RATIOS OBSERVED BY OTHER STUDIES

% MALE PROBANDS

Anencephaly	Encephalocele	Spina Bifida	Reference
25%		47%	28
26%		39%	31
44%		42%	38
29%		41%	42
27%		39%	37
32%	49%	42%	33

that the sex ratio was not different from the controls (48.6% males being affected).[33]

PARITY AND MATERNAL AGE

Conflicting reports exist for the effect of parity and maternal age on incidence of NTD, although there seems to be general agreement that the first-born has a higher risk than the second born (Carter *et al.*[28] Williamson,[31] and Czeizel *et al.*[33] Laurence,[34] and Carter *et al.*[43]). Some authors have observed U-shaped risk curves[31,33, 34] while others have noted linearly increasing risks with parity.[38] Table 3 summarizes the findings.

Parity is unavoidably entangled with maternal age. Czeizel *et al.*[33] found that the first-born has a higher risk of being affected with a NTD, and that the risk rises as the mother gets older. Leck[44] stated that in North America the incidences among first-borns are higher than those among subsequently born infants only if the mother is over age 35.

Other authors have also noted that incidences are highest among infants born to mothers less than twenty years.[28,41, 42] In one study,[45] the primaparity effect was more marked among young mothers than older mothers. Czeizel *et al.*[33] found that whereas mothers of anencephalics who are 20-24 are more numerous than expected, mothers of encephalocele affected infants are more likely to be

over 35 years of age. They also noted that paternal age was significant for encephalocele, but not anencephaly.

The conflicts in the data have been partly resolved by Elwood et al.[46] who found a U-shaped risk related to both parity and maternal age. However, they stated that the anencephaly incidence is not related to maternal age, but decreases with an increasing number of live births and increases with the number of previous stillbirths or abortions.

Czeizel et al.[33] noted a U-shaped risk for parity in the encephalocele group, and a decreasing rate with increasing parity in the A and SB groups. Tables 3 and 4 summarize the data.

ETHNIC DIFFERENCES IN NTD INCIDENCE

Ethnic origin also influences one's risks of having a child with a NTD. Ireland, Northern and Western Britain, Alexandria, Egypt, and some Sikh communities have the highest frequencies known. Northeastern North America and the Middle East have rates greater than 1/1000, whereas NTD are rare in Yemenites, Iraqis, and Iranians.

In all studies, Negroes had lower incidences of NTD than did Caucasians (3/1000 -- Caucasians, .88/1000 -- Negroes). When partitioned according to the type of defect, the anencephaly rate in Negroes was found to be

TABLE 3
INCIDENCE OF FIRST-BORNS

DEFECT IN PROBAND:	ANENCEPHALY	SPINA BIFIDA	ENCEPHALOCELE	CONTROL	STUDY
	23%	25%		28%	38
	36%			35%	44
	45%	46%		40%	28
	67%	60%	55%	48%	33
	54%	52%		38%	31

TABLE 4
INCIDENCE AT BIRTH RANKS OF 5 OR MORE

DEFECT IN PROBAND:	ANENCEPHALY	SPINA BIFIDA	ENCEPHALOCELE	CONTROL	STUDY
	28%	29%		21%	38
	36%			35%	44
	8%	10%		7%	28
	6%	5%	10%	7%	30
	0%	10%		8%	31

one sixth of the Caucasian's rates whereas the spina bifida rates were equal.[47]

The incidence of encephalocele, however, remains fairly constant, being around 1/10,000 in most populations examined, and occurring usually in the occipital region.[48] One exception is in Thailand, where an unusually high incidence of fronto-ethmoidal encephalocele has been noted.[49] (See Table 5 for a summary of the findings).

EFFECT OF MIGRATION

Indicative of genetic factors is the finding that some migrants retain the incidence of areas from which they came. For example, Indians living in Fiji have a higher incidence of anencephaly than do native Melanasians.[50] Other migrants have lower incidences than their fatherland, but higher than their adopted homeland. For example, Australians from England and Bostonians from Britain demonstrate this pattern.

However, Elwood et al.[51] demonstrated that the incidences of anencephaly among mothers of British and French origin were the same in Canada, although the incidence rates in the two countries are different (2-3/1000 in Great Britain; .5/1000 in France). The incidences among mothers of other ethnic origins were lower, and more closely resembled the incidences in their native countries. Since these groups had migrated to Canada later than did the French

TABLE 5

ETHNIC VARIATION - Incidence (per thousand)

SBC Incidence	Anencephaly inc.	Encephalocele inc.	Locale	Reference
.6	.44	.12	United States	52
1-1.5	1-1.5	-	New York	53
.77	-	-	Iowa	54
-	.6	-	S. Carolina	55
2.75	2.75	.12	Rhode Island	56
-	.6	-	Brit. Col.	57
-	.56	-	Sasketchewan	41
1.87	1.44	-	Quebec	58
-	1.33	-	New Brunswick	41
-	1.5	-	Nova Scotia	55
4.5	4.2	-	Belfast	30
4.1	3.0	.3	Wales	34
1.54	1.41	.19	London	28
-	.5	-	France	59
.72	-	-	Sweden	60
1.63	1.1	.22	Hungary	33
.6	.86	-	Israel	38
1.7	3.8	-	Egypt	61
.2	.8	.06	Nigeria	61,36,62
1.59	1.59	-	S. Africa	35
2.3	4.8	-	N. India	63
.2	.6	-	Calcutta	63
.3	.6	-	Japan	64
1.0	1.0	.1	Australia	5

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and British groups, the authors concluded that incidences in ethnic groups depended on time of migration.

FAMILY HISTORY OF NEURAL TUBE DEFECTS

Other epidemiological data has been gathered on the frequency of NTD in family members. It is evident that the risk of having a child with a NTD is dependent on the number and relationship of affected family members. The incidence of NTD among siblings of anencephalics is between 1.8 and 4.9%, and among siblings of spina bifida affected probands the incidence ranges from 2.7 to 6.1%. Czeizel et al.[33] did not find any affected siblings of encephalocele affected probands; the only affected relative of all first, second and third degree relatives (N=1288) was an uncle. However, Lorber et al.[22] found the recurrence of NTD was 6% in siblings of probands with encephalocele. Only one sibling of 356 also had an encephalocele, whereas ten had myelomeningocele (level unspecified), seven had anencephaly, and two had "other" NTD (including one with spina bifida occulta). In the data of Carter et al.[28], individuals identified as having encephaloceles had a total of 94 siblings, with two having spina bifidas, and three having anencephaly, for an incidence of 5.6%.

Early studies have suggested that siblings of NTD affected individuals were as likely to have anencephaly as to

have spina bifida (Carter et al.[43] Czeizel et al.[33] Penrose[65]); more recent studies have found that siblings tend to have the same type of defect as the proband (Cowchock et al.[66] Richards et al.[67]). Overall, among affected siblings the chances are 2:1 that the same type of defect will recur. Table 6 summarizes the findings.

In addition to siblings having an increased incidence of NTD, parents also have a greater incidence of spina bifida (anencephaly of course not being an option). Carter and Evans[68] found that 3% of parents of NTD affected individuals were themselves affected. Affected fathers had more affected offspring than did affected mothers. Three percent of half-siblings sharing the same mother as compared to 1% of half-siblings sharing the same father had NTD in the same study. Other studies have found incidences between .8 and 2.6% for half-siblings. Among other second degree relatives, incidences between 0 and 1.2% have been reported; among third degree relatives, incidences range between .25 and 2.6%. (See tables 7-9). Pooling all of the studies, the incidence among second degree relatives, excluding half-siblings, is .36% and among third degree relatives .51%.

FAMILY HISTORY OF OTHER BIRTH DEFECTS

Although isolated hydrocephalus is not generally believed to be related to NTD, a number of studies have found

TABLE 6

TYPES OF NTD IN AFFECTED SIBS

DEFECT IN PROBAND	# SIBS WITH ANENCEPHALY/T	# SIBS WITH SB/T	REFERENCE
ANENCEPHALY	2/41	0/41	31
	24/754	17/754	28
	16/708	13/708	43
	3/186	4/186	33
	18/454	8/454	67
	2/57	2/57	65
	0/66	1/66	75
	3/582	2/582	76
	8/180	5/180	77
	26/887	13/887	78
	9/278	9/278	74
	13/305	1/305	66
SPINA BIFIDA	1/119	6/119	31
	3/367	7/367	68
	12/730	13/730	28
	20/854	32/854	43
	0/334	9/334	33
	6/450	19/450	67
	2/297	8/297	65
	7/654	10/654	76
	1/123	4/123	77
	22/1256	54/1256	69
	20/903	11/903	78
	12/432	33/432	74
	4/1080	23/1080	66

TABLE 7

INCIDENCE OF NTD IN FIRST DEGREE RELATIVES

DEFECT IN PROBAND	Defect in siblings	Defect in offspring	Reference
Anencephaly/ Spina Bifida (ASB)	1.8% (19/1037)	-	53
	13% (3/23)	-	57
Anencephaly	4.5%	-	66
	4.9%	-	31
	5.2%	-	28
	4.1%	-	43
	3.8%	-	33
Spina Bifida	5.9%	-	31
	2.7%	1.9%	68
	3.4%	-	28
	6.1%	-	43
	2.6%	-	66
	2.7%	-	33
Encephalocele	6.0%	-	22
	5.6%	-	28
	0%	-	33

TABLE 8

INCIDENCE OF NTD IN SECOND DEGREE RELATIVES

DEFECT IN PROBAND	Defect in half-siblings	aunts and uncles	nieces and nephews	Reference
ASB	.8%	-	-	53
	-	.5% (3/612)	-	72
	2%	-	.3% (1/366)	73
	-	.3% (4/1170)	-	60
	-	-	-	57
Anencephaly	1.2%	-	-	28
	0%	-	-	43
	-	.2% (2/1045)	-	33
	-	.5% (4/832)	-	74
Spina Bifida	-	.7% (3/413)	-	31
	2.6%	-	-	28
	0%	-	-	43
	-	.2% (3/1769)	-	33
	-	.6% (7/1191)	-	74
Encephalocele	-	.5% (1/207)	-	33

TABLE 9

INCIDENCE OF NTD IN THIRD DEGREE RELATIVES

DEFECT IN PROBAND	Defect in Cousins	Reference
ASB	.4% (1/239)	73
	.7% (13/1899)	60
Anencephaly	2.6% (4/156)	31
	.3% (3/1129)	28
	.5% (11/2164)	43
	.3% (3/1119)	33
	.8% (13/1898)	74
Spina Bifida	.9% (4/423)	31
	.4% (6/1360)	28
	.7% (17/2474)	43
	.3% (8/2330)	33

an increased incidence among siblings of NTD probands. The highest frequency was .7%, or 9/1256 sibs of SBC probands affected with isolated hydrocephalus (Lorber[69]). Table 10 summarizes the findings of other studies.

Pooling all of the studies, the overall incidence of hydrocephalus in siblings of ASB affected probands was .24%, which is 2-4 times the population frequency (.05% Bergsma[70] or .1% Warkany[48]).

When other birth defects were considered, Czeizel and Williamson found no increases in the incidence of other birth defects in the families and sibs respectively. Carter and Evans[69] noted that among 354 sibs of index patients, 3 had congenital heart defects and one had pyloric stenosis. Richards et al.[67] found a three-fold increase in the incidences of both congenital heart defects and oral clefts among siblings. Table 11 summarizes the findings. Only cleft lip and cleft palate is significantly increased, since the incidence among siblings was almost three times the population figure. Congenital heart defects were more difficult to evaluate since the figures for population frequencies vary so widely (4/1000, Warkany[48], 8/1000, Behrman[71], and 10/1000 Bergsma[70]).

ABORTION INCIDENCE IN SIBSHIPS

Mothers of a child with a NTD may be at a higher risk of spontaneously aborting a pregnancy than mothers in the

TABLE 10

INCIDENCE OF ISOLATED HYDROCEPHALUS AMONG SIBLINGS

DEFECT IN PROBAND:	Incidence	N/T	Reference
Anencephaly/Spina Bifida	.21%	21/9794	79
	.17%	1/579	33
	.40%	5/1263	56
Total:	.232%	27/11636	
Anencephaly	.36%	1/278	74
	.14%	1/708	43
	.27%	2/754	28
	0%	0/238	31
	.17%	1/582	76
	0%	0/88	69
	.84%	1/119	80
	.56%	5/887	78
	0%	0/454	67
	.24%	1/423	59
Total:	.26%	12/4531	
Spina Bifida	0%	0/432	74
	0%	0/854	43
	0%	0/730	28
	0%	0/80	31
	.7%	9/1256	69
	.15%	1/654	76
	0%	0/166	80
	.22%	2/903	78
	0%	0/450	67
Total:	.22%	12/5525	
Grand Total:	.235%	51/21,692	
Expected:		10.846-21.692	
Significance:		$X^2 = 39.638$, $p < .001$	

TABLE 11

INCIDENCE OF OTHER BIRTH DEFECTS (N/T)

Defect	Heart		CLP		Pyloric Stenosis		Clubfoot		Reference
Defect in proband	A	SB	A	SB	A	SB	A	SB	
	ASB		ASB		ASB		ASB		
	3/354		1/354		1/354		0/354		68
	3/579		1/579		0/579		0/579		33
	4/454	7/450	5/904		0/904		0/904		67
	1/191		1/191		1/191		1/191		31
	1/278	1/432	1/278	1/432	1/278	1/432	1/278	1/432	74
	5/754	2/730	1/754	1/730	1/754	2/730	0/754	2/730	28
Totals:	10/1486	10/1612	2/1032	2/1162	2/1032	3/1162	1/1032	2/1162	
	7/1124		8/2028		2/545		1/770		
Grand Total:	27/4222		12/4222		7/4222		4/4222		
Incidence:	.64%		.28%		.17%		.09%		
Expected:	.4-1%		.15%		.4%		.1-.2%		
Significance:	NS*		$X^2 = 5.079$ $p < .05$		$X^2 = 5.812$ $p < .05$		NS		

* NS = not significant

general population. McDonald noted that the abortion risk was 3.5% higher in NTD families than in controls. She found that the abortuses in NTD sibships tended to occur earlier in the pregnancy order, as did NTD births, and unlike abortions in control sibships. This lent support to the hypothesis that those abortions are of affected fetuses.

Most of the conceptuses with a NTD are lost prior to birth. Creasy[82] found that 75% of NTD conceptuses are not born alive. Those lost at an early gestational age usually had encephaloceles, whereas those lost later usually had anencephalies. This means that 5% of all conceptions have ASB.

It has also been found that among women with a history of two or more previous miscarriages, irregardless of the number of living children, the incidence of spina bifida in the children was significantly higher, whereas the incidence of anencephaly was not.[83]

Other authors have not noted an excess of abortions in the families of NTD children, although some did not have control data, and others used general population data obtained from that data of Warburton and Fraser.[84] Table 12 summarizes the findings.

BLOOD TYPES AND HISTOCOMPATIBILITY ANTIGENS

Blood type antigesn and histocompatibility antigens and their relationship to NTD has been investigated. Coffey[85] found a higher incidence of blood type O in mothers of

TABLE 12

INCIDENCE OF ABORTION IN SIBSHIPS

Defect in Proband				
Anencephaly	ASB	Spina Bifida	Control	Reference
25.1%		25.3%	none	74
14.7%		16.2%	13%	67
16.2%		16.8%	none	43
11.0%		8.9%	none	28
16.3%		17.4%	15%*	31
22.0%		15.7%	15%*	58
11.7%		10.7%	7.5%	76
	15.6%		12.1%	80

* General population data

anencephalics; this has not been found by others. Baker and Sherry[86] noted a significant incidence of Rh- mothers in cases as compared to controls. Czeizel et al.[33] also found the increased incidence of Rh- mothers, but only in spina bifida group and not in the encephalocele and anencephaly groups. Carter et al.[28] found no significant difference for ABO or Rh, although he and others found that the incidence of Rh- mothers was higher among index groups (see Table 13).

Golding[87] noted that the greater incidence of Rh - mothers among index patients could be attributed to a dramatic increase only in mothers whose spina bifida child was the third pregnancy or later. This indicated to him that Rh isoimmunization could be etiologically significant. Table 14 summarizes the data.

Studies have examined the possible role of HLA in NTD etiology. Neither linkage studies nor examinations of associations between certain HLA types and NTD have shown a relationship between the two.[91, 92] However, one study deserves mention because of its demonstration that genetic heterogeneity among NTD is possible.

Schacter et al.[93] examined the incidence of HLA compatibility in couples who had either had a child with a NTD, had repeated pregnancy losses, or had three or more children with no abnormalities and no history of spontaneous abortions. They found that the percentage of couples sharing two or more antigens was significantly higher in couples having

TABLE 13

BLOOD GROUP DISTRIBUTIONS FROM OTHER STUDIES

	DEFECT IN PROBAND			
BLOOD TYPE	SPINA BIFIDA	ANENCEPHALY	ENCEPHALOCELE	CONTROL
A	33.5%	43.4%	37.5%	41.6%
B	19.2%	20.6%	33.3%	17.1%
O	37.9%	27.2%	25.0%	31.2%
AB	9.3%	8.8%	4.2%	10.1%
from Czeizel *et al.*[33],	N = 182	N = 136	N = 24	

BLOOD TYPE	SPINA BIFIDA	ANENCEPHALY	CONTROL
O	46.5%	45.5%	44.85%
A	39.2%	44.2%	41.41%
B + AB	14.3%	10.2%	13.74%
from Carter *et al.*[28],	N = 265	N = 226	

TABLE 14

INCIDENCE OF Rh- BLOOD TYPE
IN MOTHERS OF NTD AFFECTED OFFSPRING

% mothers Rh-	Control	Reference
15.5	15.0	80
18.8	17.0	88
25.0	14.8	33
17.8	16.0	43
18.5	17.0	90
22.6	17.2	89
32.1	15	85

two or more pregnancy losses (at similar gestational age) or a child with a NTD not compatible with life, e.g., anencephaly. This implied to the authors that only in certain cases of recurrent abortions or NTD was HLA compatibility a significant etiological factor.

ILLNESS

Research into the role of illness in the etiology of NTD has also been conducted by several investigators. In a study of influenza A and NTD, Doll[94] noticed a sharp rise in the number of stillbirths attributable to anencephaly during the same years as an Asian flu epidemic. Wilson and Stein[95] did a retrospective study in which flu titers were measured in mothers of anencephalic children and mothers with normal children. They found that 2/200 mothers with positive titers had anencephalic children, as compared to 0/188 with negative titers. The significance of these findings was unknown, although the authors concluded that flu may be occasionally associated with anencephaly. Coffey and Jessop[96] found that 34% of mothers having children born with NTD had influenza during the first trimester of pregnancy. In that same study, they noted that the incidence of NTD was 1.2% in the index group; in controls it was .9%. Similarly, Kleinebrect et al.[97] did a prospective study of the incidences of various birth defects, including NTD, in mothers having flu or febrile (fever producing) illnesses in the first twelve weeks

of pregnancy as compared to controls (unaffected mothers). In the index group the incidence of NTD was .77%, whereas in controls it was .5%. They reported that they found no significant correlations between any single anomaly and history of illness. The authors concluded that whereas fever is unlikely to be the primary cause of malformations, it may have a role in the multifactorial model of birth defects.

Kurent[47] prospectively examined the role of intrauterine infection in the etiology of NTD. The three methods were: (1) drawing serial maternal serum specimens during pregnancy, (2) determining levels of cord-serum IgM, and (3) analyzing epidemiological variables. Using serial serum specimens, the authors tested for influenzas A, B, and C, Reovirus, Mumps, ECHO 6, Respiratory synctitial, Herpes, Cytomegalic, Rubella, and several Coxsackie B viruses. No increase in the incidence of infection was noted among mothers who delivered infants with NTD as compared to mothers having normal infants.

Miller et al.[98] examined 63 pregnancies which resulted in the birth of an anencephalic. Eleven percent of the mothers had a history of hyperthermia (sauna bathing or febrile illness) near the time of anterior neuropore closure. Only .1% of controls had such a history. The authors concluded that 10% of anencephalies are caused by hyperthermia. Chance and Smith[99] questioned 43 mothers who had had a child with a spina bifida at a level of L-5 or higher; of these,

3 had had episodes of hyperthermia at the time of posterior neuropore closure. Controls, which were relatives of the mothers, had no episodes of hyperthermia. Halperin and Wilroy[100] detected 3/45 NTD births with histories of hyperthermia, including one nasal encephalocele and flu, one thoraco-lumbar myelomeningocele and pharyngitis, and one encephalocele and sauna. The incidence of hyperthermia in controls was zero.

James[101] cast doubt on the hyperthermia hypothesis by pointing out that winter conceptions are not affected as frequently as other conceptions, even though flu frequency is greater in winter; and that areas of high incidence of NTD have little correlation with hyperthermia producing occurrences. Rapola et al.[102] reported a low incidence of NTD in Finland (.32/1000 for anencephaly) although more than a million families enjoy sauna bathing (10-30 minutes at 70-100 degrees C.).

EXOGENOUS HORMONES

Exogenous hormones have been reported as possibly causing NTD. A general study of 149 mothers who had deformed infants, including 70 with NTD, revealed that 23 had had hormones administered as a pregnancy test in the first trimester, as compared to 8 of 149 controls. The authors concluded that since hormones during pregnancy caused birth defects, such pregnancy tests should be avoided.[103]

Prospective studies regarding the use of oral contraceptives and birth defects had noted no significant differences in incidences of birth defects between control and index groups (Rothman et al.[104], Ortiz-Perez et al.[105]). Kasan and Andrews[106] demonstrated that although the overall incidence of birth defects was not different between the index and control groups (2.83% vs. 2.95%), the incidence of NTD was statistically significant, being greater in the index group (.63% vs. .25%). Furthermore, only anencephaly and spina bifida, but not encephalocele or iniencephaly were greater in incidence.

Since the index group included women who had stopped taking oral contraceptives three months or less prior to conception, it is possible that oral contraceptives are not teratogenic in themselves, but rather cause some physiologic disturbance which is teratogenic. It is known that oral contraceptives cause vitamin and mineral imbalances, which is significant in light of the recent findings implicating vitamin deficiences as being etiologically involved in NTD. Smithells et al.[107] showed that the recurrence risk of NTD among vitamin supplemented women was .6%, as compared to 5% among unsupplemented women. All of the women were selected from a group who had previously had one or more children affected with NTD.

Among the nutritional imbalances caused by oral contraceptives are elevations in serum vitamin A levels, and

decreases in zinc, vitamin C and folate levels.[108] All of these have been implicated in some way in the etiology of NTD. Cohlan et al.[109] found that hypervitaminosis A produced exencephalies and spina bifidas in rates. Warkany et al.[110] demonstrated that CNS deformities were produced in rats whose mothers were fed zinc deficient diets for a short term period. In humans, Tunte[111] found an inverse correlation between ascorbated levels and incidence of anencephaly, and Hibbard and Smithells[112] found a significant relationship between NTD and defective folate metabolism in the mother.

ANTI-EMETICS

Walker[113] reported five families in which Bendectin had been given in early pregnancy. In the first family, the mother started taking anti-emetics four weeks after the last menstrual period. The result of the pregnancy was an inencephalic. In the second family, the proband had inencephaly, the oldest sibling had a defect of L-5 and the sacrum and the third child had a SBO of S-1. The second cousin also had iniencephaly, and the mother of that child had cervical spine anomalies. Both mothers had excess vomiting during those pregnancies for which anti-emetics were prescribed. In the third family, thoracic defects were noted in the proband. The level was not noted in the proband of the fourth family. In the fifth family, the proband had

iniencephaly, a paternal cousin had a thoracic myelomeningocele, and a maternal cousin had a lumbosacral myelomeningocele.

Prospective studies, however, have yielded negative results. Yerushalmy and Milkovich[114] found no instances of NTD among 330 women receiving anti-emetics during the first trimester. Similarly, Pettersson[115] noted no instances of NTD among 292 women who had been treated with meclizine. Smithells and Chinn[116] found one instance of anencephaly in offspring of 219 mothers taking anti-emetics during pregnancy. However, in a recent study by Cordero et al.[117], an association between encephaloceles and Bendectin usage was found; no association was found between other NTD and Bendectin. This study coupled with the case reports by Walker imply that anti-emetics may be significant in the etiology of some, but not all NTD.

FETAL INTERACTION

Knox[118] speculated that NTD are caused by the interaction between fetuses, either co-twins or preceding pregnancies. He first proposed that a NTD was the result of an interaction between twin fetuses, with one twin being lost, and the other affected with a NTD. He postulated the existence of a diallelic gene locus on the X chromosome, with alleles being S and T, and possible genotypes being SS, ST, and TT for females and SY and TY for males. A NTD would be

caused by the twin which possesses the allele which the other twin doesn't possess attacking the co-twin and causing its abortion. The attacker twin would then be left with a NTD. For example, in an ST/SY pair, the male twin would be aborted and the female twin left with a NTD. This theory also included sequential fetus-fetus interaction as a possible etiological event. This was supported by his finding that the mean pregnancy interval was noted to be less for infants born with NTD than for normal infants. Record et al.[76] as well found that the mean pregnancy interval was shorter for probands than controls.

Rogers[119] further expanded the hypothesis by stating that a previous abortion may also influence the next pregnancy so that a NTD occurred in that pregnancy. The residual trophoblast (rest) from the abortion would somehow become activated during the second pregnancy, and a mosaic placenta formed. However, the cellular elements derived from the previous trophoblast might be at an inappropriate stage of maturity, thus disrupting the timing of embryological events.

Clarke et al.[120] found that a significantly larger number of miscarriages and stillbirths occurred before an affected proband than after (p .001), thus supporting the hypothesis. Further support came from the findings of Arias-Bernel et al.[121] and Weisli[122] who each found XX cell lines in male anencephalics.

Contrary to this theory, however, are Clarke et al.'s[120]

finding that there was no significant difference in the mean time interval between an affected or normal child and the immediately preceding miscarriage. Further, Roberts and Lloyd[123] found an inverse relationship between the frequency of miscarriages and NTD in S. Wales. Elwood[124] found that 25% of the cases of NTD are among the firstborn.

MATERNAL FACTORS

Among maternal factors investigated include the role of fertility in NTD etiology. Knox[118] reported that pregnancies induced by clomiphene resulted in a high frequency of infants born with anencephaly. Ahlgren[125] reported a prospective study of 159 pregnancies induced by clomiphene; of the 148 infants which were liveborn, 8 had major malformations including one memingocele. The expected number of major malformations was 4-5, or half that of the observed number of malformations. Since neither the clomiphene dosage nor the number of treatments given before pregnancy markedly affected the outcome, the authors felt that the malformations were due to an underlying subfertility, and not to the clomiphene. Wynne-Davies[39] found that among mothers who had children with spina bifida, half had a history of irregular periods, long periods of infertility, menorrhagia, severe dysmenorrhea, or other menstrual disorders.

Elwood[126] disagreed with the subfertility hypothesis by comparing the dizygotic twinning rate with anencephalic

rates, which he felt were positively correlated. Since mothers of dizygous twins are more fertile, and have more pregnancies than other mothers, the correlation was puzzling. The correlation between twinning rates and NTD would be expected to be negative if mothers of anencephalics were subfertile. Therefore, he suggested that dizygotic twinning and anencephaly were related, and that clomiphene acted via a mechanism which increased the risks for both, notably by inducing twinning, which would lead to twin-twin interaction.

It is apparent from the preceding discussion that a wealth of data has been gathered and a number of theories proposed regarding the causes of NTD. It is also apparent that many contradictions exist, and there are few consistencies between the different studies.

This study was an attempt to demonstrate that the NTD are really a heterogeneous group, based on different embryological malfunctions. These malfunctions could be of at least two types, most notably neural tube non-closure and neural tube rupture. These, in turn, could have different genetic bases and environmental causes. The main questions asked by this thesis were whether such heterogeneity exists, and if so, if it can be detected by separating the NTD by location and comparing these homogeneous groups among themselves. Heterogeneity would be confirmed if there were significant differences found between the groups.

MATERIALS AND METHODS

The index group consisted of families in which one or more children were affected with a NTD. These defects included meningocele, myelomeningocele, and encephalocele. Anencephaly was not included because only four families could be ascertained. Families were selected from several sources, including the Spina Bifida Association of Michigan's mailing list, genetics clinics rosters, and private physicians.

These families were sent questionnaires which included questions about family genetic history, pregnancy history, and other background information. The family history section contained questions about incidences of other family members with NTD, hydrocephalus, scoliosis, and other "back problems", with the type to be noted. There were also questions which dealt with family history of other birth defects, most notably those which are also thought to have a multifactorial cause, including pyloric stenosis, clubfoot, congenital heart disease, and cleft lip and/or palate. There was also a notation to list individuals with Down Syndrome.

In the pregnancy history section, questions were asked about use of oral contraceptives, anti-emetics, hormones, fertility drugs, "other medication" (with a note to specify), history of any illness or vaccination during pregnancy,

history of gynecological problems, and length of time for conception to occur. The person filling out the questionnaire was also asked to note which of the mother's other pregnancies had any of those factors during the pregnancy. Family history of miscarriage and stillbirth was also obtained.

Lastly, questions were asked about ethnic origin, consanguinity, blood types of both parents, and whether or not back X-rays had been taken of either parent and the results. Information regarding the total number of first, second, and third degree relatives to the proband and sexes of siblings were also obtained.

Controls were obtained from a sample of private obstetricians' patients filling out the same questionnaire. These were matched to the proband from the index family according to parity and family size.

Medical records were requested on the proband and the mother, as well as other affected family members. The records on the proband were used in determining the type of NTD, and level when possible. The mother's medical records were used to verify pregnancy and gynecological problems. If records were not available on the proband, then the family was contacted and asked to describe the location of their child's lesion, as well as the child's abilities and which functions were affected. If the family's description of the child's function corresponded well to the location

mentioned, then the child was included in the study.

Additional data was obtained from spina bifida parents groups around the country (U.S. data). Families which consented to participate were sent a questionnaire which was modified to include a request for information regarding the location of the defect and their child's abilities. Subsequently families were included who could describe adequately the level of the lesion and which was corroborated by the description of the child's function.

RESULTS

The index patients were divided into nine groups, five from the main group of data (Michigan data) and four from the U.S. data. These were:

A. Michigan data

1. Thoracic level, including lumbo-sacral involvement
2. Lumbar level, including sacral involvement
3. Sacral level
4. "Other" level, including cervical, mid-thoracic, and mid-lumbar lesions
5. Encephaloceles

B. U.S. data

1. Thoracic level, including lumbo-sacral involvement
2. Lumbar level, including sacral involvement
3. Sacral level
4. "Other" level, including cervical, mid-thoracic, and mid-lumbar lesions

Initial comparisons were made between the same level in the Michigan and U.S. groups to determine whether the two groups of data could be pooled. The variables examined were:

1. Seasonal variation
2. Sex ratio
3. Parity
4. Ethnic origin
5. Family history of NTD
6. Family history of other birth defects
7. Number of sibs aborted
8. Blood type distributions
9. ABO and Rh incompatibility
10. Illness during pregnancy
11. Oral contraceptive use
12. Anti-emetic usage
13. Hormone usage

14. Gynecological problems
15. Inter-pregnancy gap (IPG)
16. Result of pregnancy preceding the birth of the proband

No significant differences were found between the two groups at any vertebral level, so the two bodies of data were combined for the thoracic, lumbar, sacral and other levels. See Table 15 for results of the comparisons.

The five groups were then compared to each other for each variable to test for heterogeneity. Comparisons were thoracic (T) versus lumbar (L), T versus sacral (S), T versus other (O), T versus encephalocele (E), L versus S, and so on. Comparisons were also made between each group and controls, and where possible, between probands and sibs within each group. Therefore, the comparisons made consisted of inter-group data (between index patients and controls or sibs), and intra-group data (between vertebral levels).

The statistical method used was the X^2 analysis, unless otherwise noted. When the expected number in a cell was less than five (in 2 x 2 contingency tables), Yates correction factor was applied.

TABLE 15

COMPARISONS BETWEEN MICHIGAN AND U.S. DATA - X^2 VALUES

VARIABLE EXAMINED	LEVEL T	L	S	O
SEASONAL VARIATION	0[1]	3.58[1]	.33[1]	.33[1]
SEX RATIO	.60	1.38	0	0
ABORTIONS	2.90	2.39	.30	0
PARITY	3.43	.50	.21	3.63
ABO BLOOD TYPE - MATERNAL	.38[2]	6.94[2]	.61[2]	.22[2]
ABO BLOOD TYPE - PATERNAL	2.81[2]	4.14[2]	.50[2]	3.71[2]
RH BLOOD TYPE - MATERNAL	0	1.26	.49	.45
RH BLOOD TYPE - PATERNAL	0	.41	0	0
ABO INCOMPATIBILITY	2.57	2.39	0	.49
RH INCOMPATIBILITY	0	.36	0	.50
FEBRILE ILLNESS	1.82	0	.39	.62
ORAL CONTRACEPTIVES	2.06	.89	0	.61
HORMONES	.41	2.16	.56	0
ANTI-EMETICS	.14	.19	0	.35
GYNECOLOGICAL PROBLEMS	0	1.41	0	0
INTER-PREGNANCY GAP	0[3]	0[3]	0[3]	.55[3]
CONCEPTION POST ABORTION	0	.30	.56	.34
ETHNIC ORIGIN	3.36	.15	0	0

[1] 11 degrees of freedom

[2] 3 degrees of freedom

[3] 8 degrees of freedom

All others, one degree of freedom

SEASONAL VARIATION

In order to determine whether there was any seasonality in the distribution of births of probands, the monthly incidence of births was compared to the State of Michigan data on monthly birth incidence between the years 1965-79. The NTD versus control comparison was not significant, with a X^2_{11} of 12.253. When the five levels were compared separately to the control group or their siblings, no significant differences emerged. Similarly, none of the intra-group comparisons were significant. Tables 16-17 summarize the data.

SEX RATIO

The proportion of males and females in each group and siblings of each group is given in Table 18. Although there was an apparent excess of female probands in three of the five groups, when the pooled NTD group was compared to the control group, the difference was not significant. When the index groups were separated by level, there were no significant differences noted both for inter-group and intra-group comparisons.

Since there were fewer males in the families of thoracic level probands in general, the index group and sibling group were pooled and compared to the control group. The difference was not significant, with a X^2 of 2.2 ($p > .05$). Table 19 summarizes the statistical analyses performed.

TABLE 16

MONTHLY DISTRIBUTION OF BIRTHS

MONTH : group	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	N
T	2	2	0	1	2	3	4	2	5	2	2	1	26
L	9	5	2	8	4	7	10	6	4	7	10	7	79
S	1	1	2	1	0	3	2	1	1	1	1	1	15
0	1	0	2	0	0	0	2	0	0	2	0	1	8
E	0	0	0	0	0	0	1	0	1	0	0	0	2
Control Incidence:	8.05%	7.61%	8.46%	7.97%	8.49%	8.26%	8.88%	8.85%	8.73%	8.51%	7.98%	8.19%	
sibs of:													
T	1	3	5	2	2	4	2	5	0	5	3	1	33
L	9	7	7	14	11	9	13	9	14	8	13	17	131
S	1	1	2	2	3	2	4	1	3	2	2	1	24
0	0	1	3	2	1	1	3	2	2	1	2	0	18
E	1	0	1	0	0	0	2	1	2	2	0	1	10

TABLE 17

ANALYSIS OF MONTHLY DISTRIBUTION OF BIRTHS

Comparison	X^2	Significance
NTD vs. control	12.023	NS
T vs. control	8.750	NS
L vs. control	10.178	NS
S vs. control	3.702	NS
O vs. control	12.490	NS
E vs. control	13.094	NS
T vs. L	8.340	NS
T vs. S	6.490	NS
T vs. O	14.539	NS
T vs. E	3.320	NS
L vs. S	4.530	NS
L vs. O	12.950	NS
L vs. E	9.265	NS
S vs. O	3.000	NS
S vs. E	5.818	NS
O vs. E	2.083	NS
T vs. sibs	12.17	NS
L vs. sibs	6.28	NS
S vs. sibs	3.33	NS
O vs. sibs	1.38	NS
E vs. sibs	1.60	NS

TABLE 18

SEX DISTRIBUTION

Group	Number of males	Number of females	N
T	11	18	29
L	52	52	104
S	9	13	22
O	4	9	13
E	4	3	7
Sibs of:			
T	10	18	28
L	63	53	116
S	16	9	25
O	6	10	16
E	4	7	7
Controls	31	32	63

TABLE 19

ANALYSIS OF SEX DISTRIBUTION

Comparison	X^2	Significance
NTD vs. control	.227	NS
T vs. control	1.018	NS
L vs. control	.048	NS
S vs. control	.451	NS
O vs. control	1.474	NS
E vs. control	0	
T vs. L	1.325	NS
T vs. S	.047	NS
T vs. O	.010	NS
T vs. E	.179	NS
L vs. S	.601	NS
L vs. O	1.712	NS
L vs. E	1.471	NS
S vs. O	.015	NS
S vs. E	.010	NS
O vs. E	.004	NS
T vs. sibs	.141	NS
L vs. sibs	.408	NS
S vs. sibs	2.506	NS
O vs. sibs	.143	NS
E vs. sibs	.005	NS

PARITY

The proportion of probands which were born to primagravidas and the proportion born to primaparas are given in Table 20. There was no primagravidity or primaparity effect noted in either the inter-group or intra-group comparisons. Since the index group had been matched to the control group by parity, state statistics were obtained which indicated that 33.7% of all births between 1960-1979 were first-borns. This was used as the control value. See Table 21 for a summary of the results.

SOCIAL CLASS

Social class as a variable was not examined. However, care had been taken to obtain controls from private obstetricians' offices, and since all of the index patients also had private obstetricians, the social class effect was hopefully lessened by excluding clinic patients from the control group.

ETHNIC ORIGIN

The data was divided by whether mother was of Anglo-Saxon origin or father was of Anglo-Saxon origin. No significant differences emerged in either the NTD vs. control, inter-group or intra-group comparisons. Tables 22-25 summarize the data.

TABLE 20

PROPORTION OF PROBANDS AND SIBLINGS WHICH ARE BORN TO PRIMAGRAVIDAS AND PRIMAPARAS

Group	Born to primagravidas		Born to primaparas		N
	number	percent	number	percent	
T	11	36.7%	13	43.3%	30
L	39	35.8%	45	41.3%	109
S	8	36.4%	9	40.9%	22
O	4	26.7%	7	46.7%	15
E	3	42.9%	3	42.9%	7
Sibs of:					
T	19	32.8%	14	24.1%	58
L	64	35.1%	56	29.8%	188
S	15	51.7%	11	37.9%	29
O	11	29.7%	8	21.6%	37
E	4	13.8%	4	13.8%	29

TABLE 21

ANALYSIS OF THE PRIMAPARITY AND PRIMAGRAVIDITY EFFECT

Comparison	X^2 for primaparity	X^2 for primagravidity	Significance
T vs. L	.042	.008	NS
T vs. S	.003	0	NS
T vs. O	.045	.450	NS
T vs. E	0	.092	NS
L vs. S	.016	.003	NS
L vs. O	.158	.483	NS
L vs. E	.007	.143	NS
S vs. O	.076	.068	NS
S vs. E	.009	.095	NS
O vs. E	.027	.072	NS
NTD vs. control	.005	.271	NS
T vs. control	.858	.028	NS
L vs. control	.100	.028	NS
S vs. control	.308	.412	NS
O vs. control	.162	.035	NS
E vs. control	.008	.275	NS

TABLE 22

PROPORTION OF MOTHERS WHO ARE OF ANGLO-SAXON ORIGIN

Group	Anglo-Saxon	Other	N
T	8	18	26
L	17	65	82
S	3	15	18
O	0	13	13
E	3	4	7
CONTROL	5	29	34

TABLE 23

PROPORTION OF FATHERS WHO ARE OF ANGLO-SAXON ORIGIN

Group	Anglo-Saxon	Other	N
T	8	18	26
L	13	65	78
S	4	14	18
O	1	11	12
E	1	6	7
CONTROL	4	32	36

TABLE 24

ANALYSIS OF ETHNIC ORIGIN DISTRIBUTION - MATERNAL

Comparison	X^2	Significance
T vs. control	2.239	NS
L vs. control	.275	NS
S vs. control	.034	NS
O vs. control	.873	NS
E vs. control	1.411	NS
T vs. L	1.117	NS
T vs. S	.501	NS
T vs. O	3.321	NS
T vs. E	.392	NS
L vs. S	.004	NS
L vs. O	2.023	NS
L vs. E	.764	NS
S vs. O	.871	NS
S vs. E	.739	NS
O vs. E	3.623	NS

TABLE 25

ANALYSIS OF ETHNIC ORIGIN DISTRIBUTION - PATERNAL

Comparison	X^2	Significance
T vs. control	3.737	NS
L vs. control	.599	NS
S vs. control	.458	NS
O vs. control	.074	NS
E vs. control	.058	NS
T vs. L	2.402	NS
T vs. S	.442	NS
T vs. O	1.214	NS
T vs. E	1.009	NS
L vs. S	.046	NS
L vs. O	.098	NS
L vs. E	.026	NS
S vs. O	.250	NS
S vs. E	.199	NS
O vs. E	.166	NS

FAMILY HISTORY OF NTD

The incidence of NTD in siblings, second degree relatives (half-sibs, aunts and uncles and nieces and nephews) and third degree relatives (cousins) is given in Table 26. The incidence in siblings was highest in the sacral group, and lowest in the encephalocele group. The types of defects in siblings were:

GROUP	DEFECTS IN SIBS
T	1 anencephaly
L	3 lumbosacral 1 sacral
S	1 lumbosacral 1 sacral
O	1 anencephaly
E	no affected sibs

None of the differences between the index groups were significant, nor between the pooled index groups (NTD group) and controls.

FAMILY HISTORY OF OTHER BIRTH DEFECTS

The incidence of hydrocephalus, congenital heart disease, clubfoot, pyloric stenosis and cleft lip and/or palate in first, second, and third degree relatives is shown in Tables 27 and 28. The only significant difference was that there were fewer than expected relatives affected with pyloric stenosis in the lumbar group; for the other groups as well the number of expected individuals was greater than the observed number, although the difference was not significant.

TABLE 26

FAMILY HISTORY OF NEURAL TUBE DEFECTS

GROUP	SIBLINGS		SECOND DEGREE		THIRD DEGREE	
	NUMBER AFFECTED	INCIDENCE	NUMBER AFFECTED	INCIDENCE	NUMBER AFFECTED	INCIDENCE
T	1/39	2.6%	0/164	0%	0/694	0%
L	4/152	2.6%	4/626	.6%	3/2068	.15%
S	2/25	8%	0/122	0%	2/538	.37%
O	1/24	4.2%	1/57	1.8%	0/298	0%
E	0/7	0%	0/32	0%	0/130	0%

TABLE 27

INCIDENCE OF OTHER BIRTH DEFECTS IN SIBLINGS

Group	# of sibs	Heart		Clubfoot		Pyloric		Cleft L/P		Hydrocephalus	
		obs.	exp.	obs.	exp.	obs.	exp.	obs.	exp.	obs.	exp.
T	39	0	.156-.312	0	.039-.078	0	.156	0	.0585	0	.0195-.039
L	145	3	.580-1.160	0	.145-.290	0	.580	0	.218	0	.072-.145
S	25	0	.1-.2	0	.025-.05	0	.10	0	.038	0	.0125-.025
O	21	1	.084-.168	0	.021 .042	0	.084	0	.032	0	.0155-.021
E	11	0	.044-.088	0	.011-.022	0	.094	0	.016	0	.006-.011

TABLE 28

INCIDENCE OF OTHER BIRTH DEFECTS IN FIRST, SECOND, AND THIRD DEGREE RELATIVES

Group	N	Heart obs.	Heart exp.	Clubfoot obs.	Clubfoot exp.	Pyloric sten. obs.	Pyloric sten. exp.	Cleft L/P obs.	Cleft L/P exp.	Hydrocephalus obs.	Hydrocephalus exp.
T	1236	2	4.944-9.888	4	1.236-2.472	1	4.944-	2	1.236	0	.618-1.236
L	4088	19	16.352-32.704	9	4.088-8.176	6	16.352*	2	4.088	0	2.044-4.088
S	926	3	3.704-7.408	3	.926-1.832	0	3.704	0	.926	0	.463-.926
O	553	5	2.212-4.424	2	1.106-2.212	0	2.212	2	.553	0	.276-.553
E	246	1	.984-1.968	0	.492-.984	0	.984	0	.246	1	.123-.246

*$X^2 = 6.580$, $p < .01$

FAMILY HISTORY OF ABORTION

Tables 29 and 30 summarize the data and analyses of the numbers of total pregnancies aborted in each group. Whereas no significant difference between all NTD and controls was found, when the levels were examined separately, a number of significant differences emerged. The O and E groups each had a greater incidence of abortions in sibships than did L, S or control groups. The thoracic group also had a greater incidence of abortions than did the lumbar group. These comparisons demonstrate definite heterogeneity between the encephalocele and other groups on the one hand, and the lumbar and sacral groups on the other hand. There was also heterogeneity demonstrated between the thoracic and lumbar groups.

BLOOD TYPES

A summary of ABO and Rh blood type distributions and incidence of incompatibility at the two loci appears in Tables 31-36. The distribution of A, B, AB and O phenotypes in both parents of the NTD group was significantly different than the control distributions. When partitioned and compared to each other and to controls, significant differences were found between mothers of L and O group probands and controls, and fathers of L and S group probands and controls for ABO blood type distribution (see Tables 37 and 38). To examine the nature of these differences, the data was put in the form A vs. not A, B vs. not B, O vs. not O, and AB vs. not AB (Tables 39-46 summarize the analyses). It was found

TABLE 29

INCIDENCE OF ABORTION IN SIBSHIPS

Group	Number of abortions	Number of liveborns	N
T	19	39	58
L	36	152	188
S	4	25	29
O	16	21	37
E	9	10	19

TABLE 30

ANALYSIS OF THE INCIDENCE OF ABORTION IN SIBSHIPS

Comparison	X^2 value	Significance
NTD vs. control	1.327	NS
T vs. control	3.069	NS
L vs. control	.085	NS
S vs. control	.676	NS
O vs. control	7.346	$p < .01$
E vs. control	4.966	$p < .05$
T vs. L	4.730	$p < .05$
T vs. S	3.576	NS
T vs. O	1.067	NS
T vs. E	1.320	NS
L vs. S	.479	NS
L vs. O	10.100	$p < .01$
L vs. E	6.505	$p < .02$
S vs. O	6.676	$p < .01$
S vs. E	6.552	$p < .02$
O vs. E	.086	NS

TABLE 31

MATERNAL ABO BLOOD TYPE DISTRIBUTION

BLOOD TYPE	A		B		AB		O	
Group	obs.*	exp.**	obs.	exp.	obs.	exp.	obs.	exp.
T	12	10.728	2	2.016	2	.816	8	10.440
L	23	36.207	16	6.804	6	2.754	36	35.235
S	6	6.207	3	1.260	1	.510	5	6.525
O	6	6.258	1	1.176	3	.476	4	6.090
E	3	3.129	0	.588	0	.238	4	3.045

*obs. = observed number, **exp. = expected number, based on population frequencies of ABO blood type distribution

TABLE 32

PATERNAL ABO BLOOD TYPE DISTRIBUTION

BLOOD TYPE	A		B		AB		O	
Group	obs.	exp.	obs.	exp.	obs.	exp.	obs.	exp.
T	6	8.493	3	1.596	1	1.646	9	8.265
L	24	31.737	12	5.964	5	2.414	30	30.885
S	3	7.152	4	1.344	1	.544	8	6.960
O	4	5.364	3	1.008	1	.408	4	5.220
E	2	2.235	0	.420	1	.170	2	2.175

TABLE 33

MATERNAL RH BLOOD TYPE DISTRIBUTION

Group	Rh positive obs.*	exp.*	Rh negative obs.	exp.	N
T	19	20.40	5	3.60	24
L	62	66.30	16	11.70	78
S	11	11.90	3	2.10	14
O	10	11.90	4	2.10	14
E	7	5.95	0	1.05	7
Controls	39	34.85	5	6.15	41

TABLE 34

PATERNAL RH BLOOD TYPE DISTRIBUTION

Group	Rh positive obs.	exp.	Rh negative obs.	exp.	N
T	14	15.30	4	2.70	18
L	52	54.40	12	9.60	64
S	12	10.20	0	1.80	12
O	10	10.20	2	1.80	12
E	5	4.25	0	.75	5

*obs. = observed number, exp. = expected number based on a population frequency of 15% for Rh negative blood type incidence

TABLE 35

INCIDENCE OF ABO BLOOD TYPE INCOMPATIBILITY

Group	Observed incidence	Expected incidence
T	10/19 (52.63%)	11.55/19 (60.79%)
L	45/68 (66.18%)	41.34/68 (60.79%)
S	10/14 (71.43%)	8.51/14 (60.79%)
O	9/12 (75.00%)	7.30/12 (60.79%)
E	3/5 (60.00%)	3.04/5 (60.79%)

TABLE 36

INCIDENCE OF RH BLOOD TYPE INCOMPATIBILITY

Group	Observed incidence	Expected incidence
T	6/18 (33.33%)	4.59/18 (25.5%)
L	15/61 (24.59%)	15.56/61 (25.5%)
S	2/11 (18.18%)	2.81/11 (25.5%)
O	4/12 (33.33%)	3.06/12 (25.5%)
E	0/5 (0%)	1.28/5 (25.5%)

TABLE 37

ANALYSIS OF ABO BLOOD TYPE DISTRIBUTIONS - MATERNAL

Comparison	X^2 value	Significance
NTD vs. control	22.572	$p < .001$
T vs. control	.76	NS
L vs. control	21.12	$p < .001$
S vs. control	3.234	NS
O vs. control	13.983	$p < .01$
E vs. control	1.79	NS
T vs. L	4.567	NS
T vs. S	1.214	NS
T vs. O	1.327	NS
T vs. E	2.018	NS
L vs. S	.323	NS
L vs. O	3.850	NS
L vs. E	2.586	NS
S vs. O	2.024	NS
S vs. E	2.07	NS
O vs. E	2.667	NS

TABLE 38

ANALYSIS OF ABO BLOOD TYPE DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
NTD vs. control	23.39	$p < .001$
T vs. control	2.14	NS
L vs. control	10.81	$p < .02$
S vs. control	8.09	$p < .05$
O vs. control	5.428	NS
E vs. control	4.89	NS
T vs. L	.157	NS
T vs. S	1.623	NS
T vs. O	.359	NS
T vs. E	.326	NS
L vs. S	1.610	NS
L vs. O	1.054	NS
L vs. E	1.773	NS
S vs. O	.561	NS
S vs. E	2.092	NS
O vs. E	1.890	NS

TABLE 39

ANALYSIS OF THE DISTRIBUTION OF BLOOD TYPE A - MATERNAL

Comparison	X^2 value	Significance
NTD vs. control	4.86	NS
T vs. control	.27	NS
L vs. control	7.27	$p < .01$
S vs. control	.14	NS
O vs. control	.02	NS
E vs. control	.01	NS
T vs. L	4.859	$p < .05$
T vs. S	.370	NS
T vs. O	.181	NS
T vs. E	.111	NS
L vs. S	.352	NS
L vs. O	.594	NS
L vs. E	.139	NS
S vs. O	.024	NS
S vs. E	.034	NS
O vs. E	0	NS

TABLE 40

ANALYSIS OF THE DISTRIBUTION OF BLOOD TYPE A - PATERNAL

Comparison	X^2 value	Significance
NTD vs. control	6.69	$p < .01$
T vs. control	1.32	NS
L vs. control	3.42	NS
S vs. control	4.34	$p < .05$
O vs. control	.62	NS
E vs. control	.043	NS
T vs. L	.033	NS
T vs. S	.227	NS
T vs. O	.010	NS
T vs. E	.126	NS
L vs. S	1.385	NS
L vs. O	.001	NS
L vs. E	.080	NS
S vs. O	.194	NS
S vs. E	.138	NS
O vs. E	.068	NS

TABLE 41

ANALYSIS OF THE DISTRIBUTION OF BLOOD TYPE B - MATERNAL

Comparison	X^2 value	Significance
NTD vs. control	9.52	$p < .01$
T vs. control	.0002	NS
L vs. control	13.59	$p < .001$
S vs. control	1.33	NS
O vs. control	.027	NS
E vs. control	.64	NS
T vs. L	1.667	NS
T vs. S	.332	NS
T vs. O	.017	NS
T vs. E	.621	NS
L vs. S	.0005	NS
L vs. O	.581	NS
L vs. E	.619	NS
S vs. O	.156	NS
S vs. E	.368	NS
O vs. E	.566	NS

TABLE 42

ANALYSIS OF THE DISTRIBUTION OF BLOOD TYPE B - PATERNAL

Comparison	X^2 value	Significance
NTD vs. control	15.72	$p < .001$
T vs. control	.56	NS
L vs. control	6.68	$p < .01$
S vs. control	3.92	$p < .05$
O vs. control	2.40	NS
E vs. control	.025	NS
T vs. L	.014	NS
T vs. S	.165	NS
T vs. O	.080	NS
T vs. E	.037	NS
L vs. S	.159	NS
L vs. O	.059	NS
L vs. E	.135	NS
S vs. O	0	NS
S vs. E	.347	NS
O vs. E	.285	NS

TABLE 43

ANALYSIS OF DISTRIBUTION OF BLOOD TYPE O - MATERNAL

Comparison	X^2 value	Significance
T vs. control	1.012	NS
L vs. control	.029	NS
S vs. control	.631	NS
O vs. control	1.270	NS
E vs. control	.120	NS
T vs. L	.939	NS
T vs. S	0	NS
T vs. O	.085	NS
T vs. E	.486	NS
L vs. S	.638	NS
L vs. O	1.234	NS
L vs. E	.063	NS
S vs. O	.077	NS
S vs. E	.114	NS
O vs. E	.631	NS

TABLE 44

ANALYSIS OF BLOOD TYPE O DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
T vs. control	.115	NS
L vs. control	.051	NS
S vs. control	.275	NS
O vs. control	.505	NS
E vs. control	.025	NS
T vs. L	.019	NS
T vs. S	.024	NS
T vs. O	.158	NS
T vs. E	.069	NS
L vs. S	.003	NS
L vs. O	1.012	NS
L vs. E	.156	NS
S vs. O	.778	NS
S vs. E	.401	NS
O vs. E	.068	NS

TABLE 45

ANALYSIS OF BLOOD TYPE AB DISTRIBUTION - MATERNAL

Comparison	X^2 value	Significance
T vs. control	.594	NS
L vs. control	2.834	NS
S vs. control	.487	NS
O vs. control	8.909	$p < .01$
E vs. control	.246	NS
T vs. L	.022	NS
T vs. S	.036	NS
T vs. O	.428	NS
T vs. E	.360	NS
L vs. S	.010	NS
L vs. O	1.346	NS
L vs. E	.556	NS
S vs. O	.376	NS
S vs. E	.418	NS
O vs. E	.437	NS

TABLE 46

ANALYSIS OF BLOOD TYPE AB DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
T vs. control	.201	NS
L vs. control	1.877	NS
S vs. control	.395	NS
O vs. control	.021	NS
E vs. control	.663	NS
T vs. L	.180	NS
T vs. S	.016	NS
T vs. O	.115	NS
T vs. E	.023	NS
L vs. S	.067	NS
L vs. O	0	NS
L vs. E	.005	NS
S vs. O	.045	NS
S vs. E	.002	NS
O vs. E	.463	NS

that mothers of the lumbar group probands were significantly less often of blood type A when compared to controls or the thoracic probands' mothers and significantly more often of blood type B when compared to controls. Mothers of the O group probands were significantly more often of blood type AB. Fathers of the sacral group probands were significantly less often of blood type A when compared to controls and fathers of both lumbar and sacral groups probands were more often of blood type B when compared to controls.

Rh blood type was not found to be significantly different in either NTD vs. control or inter group and intra-group comparisons. Similarly, neither ABO nor RH incompatibility were found to be significantly different in any of the comparisons. Tables 47-50 summarize these analyses.

ILLNESS

Two time spans were considered in the analysis of the effect of illness. These were the first two months, and the third through ninth month of pregnancy (see Table 51). A significantly greater number of mothers in the NTD group reported having a febrile illness during the first two months as compared to the control mothers. ($X^2 = 14.14$, $p < .001$). However, when the groups were analyzed by level, only the T, L and S groups were significantly different from controls. When probands were compared to their siblings in each group, only the T and L versus sib comparisons were significant, (see Table 52). When history of illness during the third

TABLE 47

ANALYSIS OF RH BLOOD TYPE DISTRIBUTION - MATERNAL

Comparison	X^2 value	Significance
NTD vs. control	3.18	NS
T vs. control	.64	NS
L vs. control	1.86	NS
S vs. control	.46	NS
O vs. control	2.02	NS
E vs. control	1.23	NS
T vs. L	.001	NS
T vs. S	.002	NS
T vs. O	.021	NS
T vs. E	.541	NS
L vs. S	.008	NS
L vs. O	.103	NS
L vs. E	.684	NS
S vs. O	.190	NS
S vs. E	.438	NS
O vs. E	.960	NS

TABLE 48

ANALYSIS OF RH BLOOD TYPE DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
NTD vs. control	.076	NS
T vs. control	.74	NS
L vs. control	.71	NS
S vs. control	2.12	NS
O vs. control	.026	NS
E vs. control	.88	NS
T vs. L	.108	NS
T vs. S	1.435	NS
T vs. O	.158	NS
T vs. E	.244	NS
L vs. S	.063	NS
L vs. O	.029	NS
L vs. E	.206	NS
S vs. O	.545	NS
S vs. E	0	NS
O vs. E	.021	NS

TABLE 49

ANALYSIS OF THE INCIDENCE OF ABO BLOOD TYPE INCOMPATIBILITY

Comparison	X^2 value	Significance
NTD vs. control	.982	NS
T vs. control	.530	NS
L vs. control	.826	NS
S vs. control	.665	NS
O vs. control	.503	NS
E vs. control	.001	NS
T vs. L	1.171	NS
T vs. S	1.192	NS
T vs. O	.558	NS
T vs. E	.075	NS
L vs. S	.045	NS
L vs. O	.072	NS
L vs. E	.079	NS
S vs. O	.042	NS
S vs. E	.222	NS
O vs. E	.001	NS

TABLE 50

ANALYSIS OF THE INCIDENCE OF RH BLOOD TYPE INCOMPATIBILITY

Comparison	X^2 value	Significance
NTD vs. control	.325	NS
T vs. control	.103	NS
L vs. control	.295	NS
S vs. control	.137	NS
O vs. control	.014	NS
E vs. control	.789	NS
T vs. L	.189	NS
T vs. S	.202	NS
T vs. O	0	NS
T vs. E	.858	NS
L vs. S	.005	NS
L vs. O	.094	NS
L vs. E	.528	NS
S vs. O	.124	NS
S vs. E	.041	NS
O vs. E	.720	NS

TABLE 51

HISTORY OF FEBRILE ILLNESS FOR TWO TIME SPANS

Group	Months 1-2	Months 3-9	Time unknown	No history of illness	N
T	9	1	3	18	31
L	21	4	9	74	108
S	4	1	0	18	23
O	1	0	2	12	15
E	0	0	3	4	7
Sibs of:					
T	2	0	0	34	36
L	0	2	9	131	142
S	2	1	1	21	25
O	0	0	0	21	21
E	0	0	2	6	8
Controls	0	6	1	56	63

TABLE 52

ANALYSIS OF INCIDENCE OF FEBRILE ILLNESS
DURING FIRST TWO MONTHS OF PREGNANCY

Comparison	X^2 value	Significance
NTD vs. control	13.961	$p < .001$
T vs. control	27.283	$p < .001$
L vs. control	13.965	$p < .001$
S vs. control	7.902	$p < .01$
O vs. control	.497	NS
E vs. control	.020	NS
T vs. L	1.308	NS
T vs. S	.979	NS
T vs. O	1.803	NS
T vs. E	1.298	NS
L vs. S	.006	NS
L vs. O	.723	NS
L vs. E	.667	NS
S vs. O	.216	NS
S vs. E	.302	NS
O vs. E	.524	NS
T vs. sibs	6.673	$p < .01$
L vs. sibs	30.143	$p < .001$
S vs. sibs	.298	NS
O vs. sibs	.053	NS
E vs. sibs	0	NS

through ninth months was examined, no significant differences emerged for any of the possible comparisons with X^2 being less than one for all comparisons (see Table 53). This implies that history of febrile illness during the first two months may be significant for T, L, and S level NTD.

ORAL CONTRACEPTIVES

Mothers of probands were questioned regarding oral contraceptive usage within three months of conception or during pregnancy. The only significant differences were between sibs and probands in the L group. The X^2 value was 6.607, with the corresponding significance level being .01. If oral contraceptives are significant in the etiology of certain NTD, then the effect must be small since none of the other comparisons were significant. Tables 54 and 55 summarize the data and analyses.

ANTI-EMETICS

Analysis of anti-emetic usage yielded interesting results. Whereas the NTD vs. control comparison was not significant, the T vs. control comparison was significant, with a X^2 of 4.04 and a significance level of .05. On the other had, the L vs. sib comparison was the only significant comparison among those between probands and sibs. An additional comparison was made between T sibs and L sibs, and although more sibs in the T group were exposed to anti-emetics, the difference was not significant. This then means

TABLE 53

ANALYSIS OF INCIDENCE OF FEBRILE ILLNESS HISTORY
DURING THE THIRD THROUGH NINTH MONTHS OF PREGNANCY

Comparison	X^2 value	Significance
NTD vs. control	2.742	NS
T vs. control	.458	NS
L vs. control	.965	NS
S vs. control	.110	NS
O vs. control	.497	NS
E vs. control	.020	NS
T vs. L	.016	NS
T vs. S	.047	NS
T vs. O	.494	NS
T vs. E	.232	NS
L vs. S	.021	NS
L vs. O	.439	NS
L vs. E	.312	NS
S vs. O	.699	NS
S vs. E	.314	NS
O vs. E	0	NS
T vs. sibs	.006	NS
L vs. sibs	.708	NS
S vs. sibs	.044	NS
O vs. sibs	0	NS
E vs. sibs	0	NS

TABLE 54

ORAL CONTRACEPTIVE USAGE WITHIN THREE MONTHS OF OR DURING CONCEPTION

Group	Positive history	Negative history	N
T	6	25	31
L	23	81	104
S	4	20	24
O	2	13	15
E	1	6	7
Sibs of:			
T	1	35	36
L	15	131	146
S	3	20	23
O	1	19	20
E	1	0	10
Controls	7	56	63

TABLE 55

ANALYSIS OF ORAL CONTRACEPTIVE USAGE
WITHIN THREE MONTHS OF CONCEPTION

Comparison	X^2 value	Significance
NTD vs. control	2.481	NS
T vs. control	.594	NS
L vs. control	3.224	NS
S vs. control	.113	NS
O vs. control	.076	NS
E vs. control	.063	NS
T vs. L	.108	NS
T vs. S	.028	NS
T vs. O	.105	NS
T vs. E	.097	NS
L vs. S	.347	NS
L vs. O	.195	NS
L vs. E	0	NS
S vs. O	.079	NS
S vs. E	.023	NS
O vs. E	.004	NS
T vs. sibs	3.280	NS
L vs. sibs	6.607	$p < .02$
S vs. sibs	.122	NS
O vs. sibs	.068	NS
E vs. sibs	.117	NS

that apparently more mothers of T probands used anti-emetics during all pregnancies, whereas L mothers tended to use anti-emetics more often during the pregnancies which resulted in affected offspring. See Tables 56 and 57 for data and analyses.

HORMONES

Whereas the NTD vs. control comparison was not significant, two significant differences emerged when hormone usage during pregnancy was analyzed for each level. Mothers of O group probands reported using hormonal preparations more often during pregnancy than did mothers of the L or control groups. No other comparisons were significant (see Tables 58 and 59).

GYNECOLOGICAL PROBLEMS

No significant differences emerged for either NTD vs. control, inter-group or intra-group comparisons when mothers were evaluated for history of hormone influenced gynecological problems. Tables 60 and 61 summarize the data and analyses.

INTER-PREGNANCY GAP (IPG)

The NTD vs. control comparison was not significant. However, when levels were examined separately, the L vs. O, L vs. E, S vs. O, and S vs. E comparisons were significant. Probands of the O and E groups were conceived within three months of a preceding pregnancy more often than L or S

TABLE 56

HISTORY OF ANTI-EMETIC USAGE DURING PREGNANCY

Group	Positive history	Negative history	N
T	12	19	31
L	28	78	106
S	4	18	22
O	6	9	15
E	4	3	7
Sibs of:			
T	9	28	37
L	18	125	133
S	1	22	23
O	2	20	22
E	7	2	9
Controls	12	51	63

TABLE 57

ANALYSIS OF ANTI-EMETIC USAGE DURING PREGNANCY

Comparison	X^2 value	Significance
NTD vs. control	1.755	NS
T vs. control	4.225	$p < .05$
L vs. control	1.185	NS
S vs. control	.008	NS
O vs. control	1.932	NS
E vs. control	3.249	NS
T vs. L	1.754	NS
T vs. S	2.571	NS
T vs. O	.007	NS
T vs. E	.302	NS
L vs. S	.659	NS
L vs. O	.622	NS
L vs. E	1.729	NS
S vs. O	1.188	NS
S vs. E	2.321	NS
O vs. E	.568	NS
T vs. sibs	1.635	NS
L vs. sibs	16.775	$p < .001$
S vs. sibs	1.003	NS
O vs. sibs	3.370	NS
E vs. sibs	.114	NS

TABLE 58

HISTORY OF HORMONE USAGE DURING PREGNANCY

Group	Positive history	Negative history	N
T	3	28	31
L	8	98	106
S	2	22	24
O	5	10	15
E	2	5	7
Sibs of:			
T	2	34	36
L	9	135	144
S	0	23	23
O	2	19	21
E	0	9	9
Controls	3	60	63

TABLE 59

ANALYSIS OF HORMONE USAGE DURING PREGNANCY

Comparison	X^2 value	Significance
NTD vs. control	2.115	NS
T vs. control	.218	NS
L vs. control	.150	NS
S vs. control	.016	NS
O vs. control	7.868	$p < .01$
E vs. control	2.393	NS
T vs. L	0	NS
T vs. S	.030	NS
T vs. O	2.461	NS
T vs. E	.513	NS
L vs. S	.017	NS
L vs. O	6.622	$p < .02$
L vs. E	1.428	NS
S vs. O	2.428	NS
S vs. E	.015	NS
O vs. E	.051	NS
T vs. sibs	.030	NS
L vs. sibs	1.907	NS
S vs. sibs	.565	NS
O vs. sibs	2.018	NS
E vs. sibs	.907	NS

TABLE 60

HISTORY OF HORMONE-RELATED GYNECOLOGICAL PROBLEMS

Group	Positive history	Negative history	N
T	1	30	31
L	7	91	98
S	3	19	22
O	3	12	15
E	2	5	7
Controls	3	60	63

TABLE 61

ANALYSIS OF MATERNAL HISTORY OF GYNECOLOGICAL PROBLEMS

Comparison	X^2 value	Significance
NTD vs. control	1.320	NS
T vs. control	.124	NS
L vs. control	.076	NS
S vs. control	.844	NS
O vs. control	2.105	NS
E vs. control	3.565	NS
T vs. L	.752	NS
T vs. S	.786	NS
T vs. O	1.783	NS
T vs. E	2.279	NS
L vs. S	.324	NS
L vs. O	1.311	NS
L vs. E	1.582	NS
S vs. O	.004	NS
S vs. E	.113	NS
O vs. E	.119	NS

probands. In addition, O probands were conceived within 7 months more often when compared to their normal sibs. This implies that a short IPG (less than three months) may be etiologically related to certain types of NTD (see Tables 62 and 63).

CONCEPTION AFTER ABORTION

The NTD vs. control comparison was not significant; however, the L vs. O, S vs. O, and O vs. control comparisons were significant. There were more probands of the O group conceived following an abortion. See Tables 64 and 65 for data and analyses summaries.

In all comparisons, no significant differences were found between the L and S groups or between the O and E groups. This implies that there was no heterogeneity which could be detected between those two pairs of groups, so that they could be pooled for the purpose of analysis. Comparisons were then repeated pooling lumbar and sacral groups (LS), and the other and encephalocele groups (OE). As before, no significant differences were observed for seasonal variation, ethnic origin, sex ratio, parity effect, NTD family history, Rh blood type distribution, or ABO and Rh incompatibility (see Table 66). However, differences were found among the groups for the other variables, and these will be discussed separately.

TABLE 62

INTER-PREGNANCY GAP IN MONTHS

Number of months between pregnancies: Group	1	2	3	4	5	6	7	8+	N
T	0	0	1	0	0	0	0	16	17
L	1	0	1	4	0	2	1	41	50
S	0	0	0	0	0	1	0	13	14
O	2	0	1	0	0	0	1	44	8
E	1	0	1	0	1	0	0	11	4
Controls	1	0	3	4	0	3	0	28	39

TABLE 63

ANALYSIS OF INTER-PREGNANCY GAP BY MONTHLY INCREMENTS

Comparison	≤1 mos.	≤2 mos.	≤3 mos.	≤4 mos.	≤5 mos.	≤6 mos.	≤7 mos.	≤8 mos.
T vs. control	0	0	.006	1.20	1.20	2.34	2.34	2.25
L vs. control	0	0	1.417	1.17	1.17	1.94	.80	.73
S vs. control	0	0	.576	1.50	1.50	.75	.75	.79
O vs. control	2.5	2.5	2.036	.15	.15	.27	.10	.10
E vs. control	.67	.67	2.037	.28	2.48	2.42	2.42	2.41
T vs. L	0	0	.004	.85	.85	.29	1.07	1.03
T vs. S	0	0	.004	0	0	0	0	0
T vs. O	1.70	1.70	2.254	.25	.25	.25	.25	.375
T vs. E	1.02	1.02	2.183	.375	3.0	3.0	3.0	3.0
L vs. S	0	0	.360	.30	.30	.16	.16	0
L vs. O	3.50	3.50	8.381*	2.53	2.53	.15	1.33	1.33
L vs. E	.89	.89	6.210*	.29	2.52	2.17	2.45	2.48
S vs. O	1.33	1.33	3.857*	3.38	3.38	3.00	1.88	1.69
S vs. E	.84	.84	4.201*	.50	3.38	3.00	3.00	.81
O vs. E	0	0	.171	0	.19	.19	2.7	2.7
T vs. sib	.573	.132	.573	0	0	2.14	2.14	2.77
L vs. sib	.011	.12	.302	.89	.26	1.22	.75	.96
S vs. sib	0	.73	.909	.73	1.90	.502	.502	.04
O vs. sib	1.96	1.96	.745	2.24	2.24	2.24	4.456*	2.77
E vs. sib	.016	.016	1.387	1.05	2.77	.96	.96	.96

*Significant findings

TABLE 64

PROPORTION OF CONCEPTIONS OCCURRING AFTER ABORTIONS AMONG PROBANDS AND SIBLINGS

Group	Conception after abortion	Conception after livebirth	N
T	8	23	31
L	15	90	105
S	2	22	24
O	7	8	15
E	3	4	7
Sibs of:			
T	4	34	38
L	15	130	145
S	1	22	23
O	0	20	20
E	2	9	11
Control	9	54	63

TABLE 65

ANALYSIS OF DISTRIBUTION OF CONCEPTION
OCCURRING AFTER ABORTION

Comparison	X^2 value	Significance
NTD vs. control	.777	NS
T vs. control	1.752	NS
L vs. control	0	NS
S vs. control	.149	NS
O vs. control	5.937	$p < .02$
E vs. control	1.889	NS
T vs. L	2.260	NS
T vs. S	1.726	NS
T vs. O	1.166	NS
T vs. E	.226	NS
L vs. S	.297	NS
L vs. O	7.115	$p < .01$
L vs. E	2.136	NS
S vs. O	5.632	$p < .02$
S vs. E	2.564	NS
O vs. E	.028	NS
T vs. sibs	2.775	NS
L vs. sibs	.896	NS
S vs. sibs	.312	NS
O vs. sibs	1.192	NS
E vs. sibs	.528	NS

TABLE 66

NON-SIGNIFICANT COMPARISONS USING POOLED DATA - X^2 VALUES

Variable	LS v. C*	OE v. C	T v. LS	T v. OE	LS v. OE	LS v. sibs	OE v. sibs
Seasonal	10.570	3.940	10.710	13.670	9.098	1.140**	1.33**
Sex ratio	.011	.515	1.041	.021	.490	1.547	.043
Primagravidity effect	.278	.035	.007	.132	.037	.010	.198
Primaparity effect	.005	1.375	.044	.023	.139	-	-
Rh blood type - maternal	2.305	.046	0	.022	.027	-	-
Rh blood type - paternal	.037	.011	.093	.136	.002	-	-
ABO incompatibility	1.354	.683	1.402	1.216	.079	-	-

*Control

**Compared seasonally

TABLE 66 (cont'd)

Variable	LS v. C*	OE v. C	T v. LS	T v. OE	LS v. OE	LS v. sibs	OE v. sibs
Rh incompatibility	.601	.013	.295	.071	0	-	-
Ethnic origin maternal	.468	.001	1.385	.817	.043	-	-
Ethnic origin paternal	.852	.004	2.244	1.559	1.369	-	-

*Control

ABORTIONS IN SIBSHIPS

Pooled comparisons showed that OE vs. control, T vs. LS, and LS vs. OE comparisons were significant. The T and OE groups each had an elevated rate of abortions. See Table 67 for analyses.

FAMILY HISTORY OF BIRTH DEFECTS

When the data were pooled, the only significant difference in the incidence of birth defects was that fewer relatives of LS probands were affected with pyloric stenosis than expected. The X^2 value was 9.893 ($p < .01$).

BLOOD TYPES - ABO

The blood type distribution was significantly different in that more mothers and fathers of LS group probands were blood type B and fewer were blood type A when compared to expected population values. Mothers of OE probands were significantly more of ten blood type AB when compared to controls. Tables 68-77 summarize the findings.

ILLNESS

Pooled data comparisons showed that the LS vs. sib and the LS vs. control comparisons were significant in that mothers of LS probands reportedly had more febrile illness during the first two months of pregnancy. In addition, the T vs. OE comparison was significant, with T probands' mothers reporting more instances of febrile illness during

TABLE 67

ANALYSIS OF POOLED DATA FOR ABORTION INCIDENCE IN SIBSHIPS

Comparison	X^2 value	Significance
LS vs. control	.211	NS
OE vs. control	10.631	$p < .001$
T vs. LS	5.573	$p < .02$
T vs. OE	1.698	NS
LS vs. OE	16.856	$p < .001$

TABLE 68

ANALYSIS OF MATERNAL BLOOD TYPES - POOLED DATA

Comparison	X^2 value	Significance
LS vs. control	23.631	$p < .001$
OE vs. control	7.941	$p < .05$
T vs. LS	4.082	NS
T vs. OE	.765	NS
LS vs. OE	4.199	NS

TABLE 69

ANALYSIS OF PATERNAL BLOOD TYPES - POOLED DATA

Comparison	X^2 value	Significance
LS vs. control	17.102	$p < .001$
OE vs. control	5.828	NS
T vs. LS	.171	NS
T vs. OE	.826	NS
LS vs. OE	.760	NS

TABLE 70

ANALYSIS OF BLOOD TYPE A DISTRIBUTION - MATERNAL

Comparison	X^2 value	Significance
LS vs. control	8.156	$p < .01$
OE vs. control	.163	NS
T vs. LS	3.348	NS
T vs. OE	.229	NS
LS vs. OE	1.256	NS

TABLE 71

ANALYSIS OF BLOOD TYPE A DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
LS vs. control	6.573	$p < .01$
OE vs. control	.608	NS
T vs. LS	.002	NS
T vs. OE	.056	NS
LS vs. OE	.113	NS

TABLE 72

ANALSYSIS OF BLOOD TYPE B DISTRIBUTION - MATERNAL

Comparison	X^2 value	Significance
LS vs. control	15.741	$p < .001$
OE vs. control	.361	NS
T vs. LS	1.042	NS
T vs. OE	.229	NS
OE vs. LS	.055	NS

TABLE 73

ANALYSIS OF BLOOD TYPE B DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
LS vs. control	11.290	$p < .001$
OE vs. control	1.890	NS
T vs. LS	.028	NS
T vs. OE	.022	NS
LS vs. OE	.006	NS

TABLE 74

ANALYSIS OF BLOOD TYPE O DISTRIBUTION - MATERNAL

Comparison	X^2 value	Significance
LS vs. control	.024	NS
OE vs. control	.004	NS
T vs. LS	0	NS
T vs. OE	.580	NS
LS vs. OE	.109	NS

TABLE 75

ANALYSIS OF BLOOD TYPE O DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
LS vs. control	.001	NS
OE Vs. control	.466	NS
T vs. LS	.086	NS
T vs. OE	.538	NS
LS vs. OE	.416	NS

TABLE 76

ANALYSIS OF BLOOD TYPE AB DISTRIBUTION - MATERNAL

Comparison	X^2 value	Significance
LS vs. control	3.321	NS
OE vs. control	4.664	$p < .05$
T vs. LS	0	NS
T vs. OE	0	NS
LS vs. OE	.852	NS

TABLE 77

ANALYSIS OF BLOOD TYPE AB DISTRIBUTION - PATERNAL

Comparison	X^2 value	Significance
LS vs. control	2.262	NS
OE vs. control	.759	NS
T vs. LS	.067	NS
T vs. OE	.010	NS
LS vs. OE	.475	NS

the first two months. See Table 78.

ORAL CONTRACEPTIVES

Pooled data analysis revealed that more mothers of LS probands reported oral contraceptive usage within three months of conception when compared to normal sibs. No other comparisons were significant (Table 79).

ANTI-EMETICS

Whereas only the L vs. sib and T vs. control comparisons were significant when each group was examined separately; when the groups were combined, not only was the LS vs. sib comparison significant, but the LS vs. OE and OE vs. control comparisons were significant as well. An additional comparison was made between siblings of each group and it was noted that LS mothers significantly less often took anti-emetics during normal pregnancies than did T or OE mothers. Table 80 summarizes the analyses.

HORMONES

The LS vs. OE and OE vs. control comparisons were significant. In addition, the OE vs. sib comparison was significant. The results of analyses are summarized in Table 81.

GYNECOLOGICAL PROBLEMS

When pooled data was used, the OE vs. control comparison was significant, in that more mothers of OE probands

TABLE 78

ANALYSIS OF POOLED DATA FOR FEBRILE ILLNESS

Comparison	X^2 value	Significance
LS vs. control	13.798	$p < .001$
OE vs. control	.306	NS
T vs. LS	1.496	NS
T vs. OE	9.666	$p < .01$
LS vs. OE	1.887	NS
LS vs. sibs	28.505	$p < .001$
OE vs. sibs	.025	NS

TABLE 79

ANALYSIS OF POOLED DATA FOR ORAL CONTRACEPTIVE USAGE

Comparison	X^2 value	Significance
LS vs. control	2.877	NS
OE vs. control	.100	NS
T vs. LS	.046	NS
T vs. OE	.031	NS
LS vs. OE	.270	NS
LS vs. sibs	6.178	$p < .02$
OE vs. sibs	.166	NS

TABLE 80

ANALYSIS OF POOLED DATA FOR ANTI-EMETIC USAGE DURING PREGNANCY

Comparison	X^2 value	Significance
LS vs. control	.844	NS
OE vs. control	5.928	$p < .05$
T vs. LS	3.183	NS
T vs. OE	.241	NS
LS vs. OE	3.897	$p < .05$
LS vs. sibs	9.261	$p < .01$
OE vs. sibs	1.509	NS
T sibs vs. LS sibs	4.221	$p < .05$
LS sibs vs. OE sibs	5.262	$p < .05$
T sibs vs. OE sibs	.192	NS

TABLE 81

ANALYSIS OF POOLED DATA FOR HORMONAL USAGE DURING PREGNANCY

Comparison	X^2 value	Significance
LS vs. control	.284	NS
OE vs. control	9.627	$p < .01$
T vs. LS	.133	NS
T vs. OE	2.801	NS
LS vs. OE	8.727	$p < .01$
LS vs. sibs	.648	NS
OE vs. sibs	4.212	$p < .05$

had hormonal types of gynecological problems than did controls. See Table 82.

IPG

Additional differences emerged for analysis of this variable. Whereas only the T vs. O, T vs. E, and S vs. O comparisons were significant when groups were examined separately, combining the groups yielded significant differences for T vs. OE, LS vs. OE, OE vs. sibs, and OE vs. control comparisons. In each case, probands of the OE group had shorter IPG's than did probands of the T or LS groups, controls, or sibs. See Table 83.

CONCEPTION AFTER ABORTION

The LS vs. OE, OE vs. control, and OE vs. sib comparisons were significant, as more OE probands were conceived after an abortion. The analyses are given in Table 84.

In summary, it was shown that heterogeneity exists between NTD when separated by location of defect. Lumbar and sacral defects appeared to be one homogeneous group, whereas encephalocele and other level defects appeared to be a second homogeneous group. This was done by X^2 analysis of contingency tables and demonstrating that dependence on classification exists.

TABLE 82

ANALYSIS OF POOLED DATA FOR HISTORY OF GYNECOLOGICAL PROBLEMS

Comparison	X^2 value	Significance
LS vs. control	.448	NS
OE vs. control	4.584	$p < .05$
T vs. LS	.346	NS
T vs. OE	3.125	NS
LS vs. OE	2.695	NS

TABLE 83

ANALYSIS OF IPG OF LESS THAN OR EQUAL TO THREE MONTHS - POOLED DATA

Comparison	X^2 value	Significance
LS vs. control	1.135	NS
OE vs. control	4.255	$p < .05$
T vs. LS	.286	NS
T vs. OE	3.505	NS
LS vs. OE	13.641	$p < .001$

TABLE 84

ANALYSIS OF POOLED DATA FOR DISTRIBUTION OF CONCEPTIONS OCCURRING AFTER AN ABORTION

Comparison	X^2 value	Significance
LS vs. control	.149	NS
OE vs. control	7.847	$p < .01$
T vs. LS	2.141	NS
T vs. OE	2.214	NS
LS vs. OE	11.325	$p < .001$
LS vs. sibs	2.021	NS
OE vs. sibs	9.387	$p < .01$

DISCUSSION

SEASONAL VARIATION

Most authors have noted seasonal variation in NTD incidences. A few studies have shown that the seasonal patterns change from year to year, and others have shown that not all NTD show the same pattern or variation. In the present study, no significant variation was found when the NTD group was compared to controls, although there appeared to be a higher incidence in the last half of the year as compared to the first half of the year. When the NTD group was examined by defect location, no significant differences emerged. There are four possible reasons for the failure to detect a seasonal effect. One, the numbers of probands were too small to detect an effect; second, a seasonal pattern which shifts from year to year would not be detected; third, a local seasonal effect may be undetected because of the inclusion of national data; fourth, no seasonal effect exists. It is not possible to discern between the different possibilities.

SEX RATIO

No significant differences between sex ratios in any of the groups were found, although numberically there were fewer males than females in three of the five groups. Other

studies cited had found fewer males than females affected with NTD, with the percentage of males ranging between 39% and 47% for spina bifida, and 25% and 44% for anencephaly. In almost all studies, the percentage of male probands was less in the anencephaly group than in the spina bifida group. In the present study, the percentage of male probands in the NTD group was 45.7%, which is within the range cited. However, neither the lumbar group nor the encephalocele group had an excess of affected females. The equal sex distribution in the encephalocele group is supported by Czeizel's finding of a sex ratio of 49%. The equal sex ratio in the lumbar group can be explained by the observation of Nightingale et al.[127] that whereas more spina bifida affected females are born, the mortality is higher in females. Since this study's population was obtained mostly from spina bifida parents' groups, it is not surprising that the sex ratio was equal, since almost all of the probands were still alive.

PARITY

The present study did not find a significantly greater incidence of first-born probands. This finding is not in accordance with the findings of Carter et al.[28], Williamson[31], and Czeizel et al.[33], who each noted a greater incidence of probands which were first liveborn. The most likely explanation is that the numbers in the present study were too small to detect a significant parity effect, since the percentage of probands which were the first-born was

greater than the control percentage in all instances.

The earlier studies used, as control data, population figures of first-born incidence. Since families of NTD affected individuals are known to differ epidemiologically from other families (i.e., greater abortion incidence, lower social class, different ethnic origin, etc.), a more valid method would be to derive the proportion of first-borns and first pregnancies from the NTD families themselves, and then determine if the probands follow the same distribution pattern. When Williamson's, Carter's and Czeizel's data are analyzed in this manner, it is found that in Williamson's and Carter's studies, there were fewer first-borns in the index families than in the control group; in Czeizel's data, there were fewer first-borns in the anencephaly and encephalocele families but more in the spina bifida families. As a result, the only alterations in the findings were that SBC's were significantly more often first-born whereas anencephalics were not in Williamson's study. In the present study, there were more first-borns in the index families than in the control group, so the seeming excess of first-borns in the index group as compared to the control group disappears.

When the data in the present study were examined regarding pregnancy order, the probands were not significantly more often the first pregnancy. Carter's and Williamson's data could be examined for this aspect, and it was found that their data showed that the proband was not significantly

more often the first pregnancy (see Table 85).

It becomes apparent that it is not the first pregnancy which increases the risk, but rather the first-born. The inference is that the abortion rate must be higher among the early pregnancies. If one accepts the findings of Record et al.[76], who found that the risk of NTD goes up with increasing livebirths, then the postulate that these aborted fetuses are also affected with NTD is valid, i.e., subsequently born sibs would be expected to have a higher risk of themselves being affected with a NTD.

There is still no explanation why the liveborn and aborted fetuses occur earlier in the pregnancy order rather than randomly. It is clear that a parity effect exists in some populations, what the basis is for this effect is obscure.

ETHNIC ORIGIN

The role of ethnic origin was examined by comparing the incidence of Anglo-Saxon ancestry among mothers and fathers of probands. Although it has been reported that migrants from regions of high incidence have a higher risk than persons in the same area who are from regions of low incidence, it has been shown that the time of immigration is important, and determines the rate based on ethnic origin. Since that information was not elicited by this study, a meaningful analysis could not be made. Although the T group had more

TABLE 85

PRIMAPARITY EFFECT USING INDEX FAMILIES FOR DETERMINATION OF EXPECTED INCIDENCE OF FIRST-BORNS

Study	Incidence of first-borns in: Controls	Index families	Significance: V. Controls	V. Index families
Williamson -	A 37.88	37.33	2.81	1.94
"	SB 37.88	34.94	4.21*	44.36**
Carter	41.71	36.96	.168	.168
Czeizel -	A 47.9	44.81	48.56**	29.248**
"	SB 47.9	51.55	31.77**	7.12 ***
"	Ë 47.9	42.16	.011	2.690

*p < .05

**p < .001

***p < .01

parents of Anglo-Saxon origin, that incidence was not significant.

FAMILY HISTORY OF NTD

Overall, the incidence of NTD in family members was 3.2% of sibs, .5% of second degree, and .1% of third degree relatives being affected. Previous studies had found incidences among siblings of spina bifida probands being between 2.6% and 6.1%. In U.S. studies, Cowchock et al.[66] found that the incidence of NTD among siblings of probands with spina bifida was 2.5%. Janerich noted a recurrence risk of 1.8%. Neither figure is significantly different from the present study (X^2values = .43 and 2.00 respectively).

In the studies in which encephaloceles were examined separately, incidences were 0%[33], 5.6%[43], and 6.0%[22]. Holmes et al.[128] made the point that inclusion of Meckel's Syndrome will artificially increase the recurrence risk, since Meckel's Syndrome is an autosomal recessive disorder and has a recurrence risk of 25%. Neither Lorber et al.[22] nor Carter et al.[43] make any mention of any consideration being given to ruling out Meckel's Syndrome in their data collection. Since Holmes et al.[128] found that 4.7% of all NTD (in the U.S.) are caused by Meckel's Syndrome, and encephaloceles are 10% of all NTD (in the U.S.), then the inference can be made that 21% of encephaloceles are due to Meckel's Syndrome (provided that Meckel's Syndrome always has an encephalocele as opposed to some other NTD). If this

were the case, then the recurrence risk among sibs of encephalocele affected individuals (without making the distinction between Meckel's and "multifactorial" cases) would be 5.3%, if the "multifactorial" cases had a 0% recurrence risk. The risk would change based on the actual proportion of Meckel's cases which have an encephalocele and the risk to the sibs of the "multifactorial" cases.

Among second degree relatives, the incidences in the literature ranged from .2 - .5%, with a pooled value of .4%. In the present study, the incidence among second degree relatives was .5%, not significantly different from the pooled value (X^2 = .061). Among third degree relatives, reported incidences ranged from 0% to .7%, with a pooled value of .5%. The present study found an incidence of .1% for third degree relatives, which is significantly less than the pooled value (X^2 = 10.358, $p < .002$). The reason for this difference is that the published incidences are almost exclusively from Great Britain, where a higher risk of NTD exists among the relatives.

In addition to the actual numerical risk figures, it is important to note that in the present study, affected siblings of lumbo-sacral affected individuals also had lesions of the lumbo-sacral area, whereas affected siblings of T and OE affected individuals had anencephaly. Although previous studies had found that siblings of affected individuals were almost as likely to have anencephaly as spina bifida,

Cowchock et al.[66] illustrated that the defect in affected siblings is usually the same as that in the proband. This implies that either siblings of more severely affected individuals tend to be more severely affected themselves, in keeping with the multifactorial model; or that heterogeneity exists among the NTD and families are prone to only one type of NTD, possibly on an embryological basis.

FAMILY HISTORY OF ABORTION

Some studies have noted a slight increase in the incidence of abortions in sibships (McDonald[81], Record et al.[76]), while others (Carter[28], Richards[67], Williamson[31], and Lippman-Hand et al.[38]) have not. Overall, the incidence of abortions in the NTD group was 25.4% as compared to 20.51% in the controls; when probands are also considered, then the percentage of pregnancies aborted was 16.4% among the index group and 13.1% among the controls. However, the T and OE, but not the LS groups accounted for the increased incidence of abortions, with that increased incidence being significant. These data are difficult to compare to previous studies, since either control data were not given, or the general population abortion incidence of 15% was given for comparison. When the percentage of siblings which were aborted was calculated, the derived figure was not a representation of the mother's reproductive history since the proband, which was always a term pregnancy, was not included in the calculation. Therefore, the number of term pregnancies were

not taken into account when deriving the abortion incidence. When probands were included in the calculated incidence of abortion, this could not be compared, since the population figure includes couples all of whose pregnancies have aborted, whereas the index group is biased because the mother has had at least one term pregnancy.

In the two studies which did obtain comparable data, it was shown that the incidence of abortion among siblings is 3.5 - 4.2% greater when the index patient has a NTD. In the present study, the incidence of abortion in the NTD group was 4.8% greater than in the controls (not significant) and was attributable solely to families of probands of T, O and E type defects (individually significant). The difference in the present study is based on the larger contribution from families with T, E and O level defects. Since other studies had pooled all NTD, it can be speculated that whether or not abortion incidence is significant in that study depends on the proportion of the total sample made up of the subgroups with high abortion rates. This study clearly demonstrates that the overall small increase in abortion rates is attributable to small subgroups of NTD.

Although it is apparent that the abortion incidence is higher in OE and T sibships than in LS sibships, it cannot be discerned whether the basis for the excess is the same in the two groups. Since a suggestion had been made that excess abortions in sibships are similarly affected fetuses,

and that affected males may be more likely to miscarry than affected females, the paucity of males and excess of abortions in T sibships may be due to affected males being miscarried. Since OE sibships had an almost equal sex distribution among probands and sibs, it is likely that the basis for the excess abortions in these sibships is different.

FAMILY HISTORY OF OTHER DEFECTS

In the present study, none of the siblings of any proband group were reported as having isolated hydrocephalus, although previous studies have indicated that the incidence of hydrocephalus is increased among siblings of NTD probands. However, the small number of siblings in each of the present groups was the most likely explanation for this lack. The expected number of affected siblings with hydrocephalus would be .54, given the observed incidence of .22% among siblings of NTD affected individuals.

The incidence of other birth defects with a multifactorial cause has also been noted by other studies. Combining the findings from prior studies, it was apparent that oral clefting may be the most likely to be increased in the siblings of NTD affected individuals. However, no increase in clefts was noted among sibs of any of the groups, perhaps due to the small sample size. The expected number of affected siblings was 1.04, given the observed incidence of .42% found by other studies.

Since the incidences of both hydrocephalus and clefting, although significantly increased, are still small, it would be pertinent to further characterize the families with both NTD and the above-mentioned defects. It may be possible that hydrocephalus is more likely to occur in siblings of probands whose NTD is of a rupture type of defect, which could be the smaller subgroup of NTD. Since clefting and NTD have had similar environmental factors suggested as being important (e.g., folate deficiency, hyperthermia, hormone imbalance), it can be postulated that there exist genes which confer susceptibility to a specific teratogen, and that the type of defect depends on the timing of the insult. In this case a genetic component could be concerned with neural tube and lip and palate closure (both mid-line closure processes). The only significant finding in the present study was that fewer than expected relatives of LS affected individuals had pyloric stenosis.

In previous studies as well, there was a small deficiency of pyloric stenosis affected siblings, although the difference was not significant. The reason for this is unknown, and whether it is due to under-reporting by the relatives, as opposed to a genuine negative relationship between the two defects cannot be discerned at this point.

BLOOD TYPES

Since some studies had found higher incidences of blood type O in mothers of anencephalics, and others had found higher incidences of mothers having Rh- blood type, the data from the present study were examined. Mothers and fathers of the LS group were reportedly more often of blood type B and less often of blood type A than expected. Although the studies by Carter *et al.*[43] and Czeizel *et al.*[33] noted no significant differences in blood type distribution, when index groups were compared to controls, both studies showed fewer mothers of spina bifida affected individuals having blood type A. When Carter's and Czeizel's data were put in the form A vs. not A, the numbers were:

Carter	A	not A	Czeizel	A	not A
observe	104	161		61	121
expect	110	155		76	106
	$X^2 = .56$, NS			$X^2 = 5.08$, $p < .05$	

Since Carter included encephaloceles with the spina bifida group, it is possible that his data may not be comparable.

Since the incidence of blood type A is the same in Great Britain as it is in the U.S., a higher proportion of individuals in the index group would not account for the skewed blood type distribution. Therefore the reason for this finding is unclear, but since the deficiency exists in Carter and Czeizel's data, further investigation is merited.

Baker and Sherry[86] found the incidence of Rh- blood to

be higher in mothers having children with a NTD (n=28, significant at the .02 level). Czeizel et al.[33] found the incidence of Rh- blood type in mothers of spina bifida probands was 25%, whereas it was not significantly increased in mothers of anencephalics or encephaloceles. Other authors have noted an increased incidence of Rh- blood type in mothers of SBC affected offspring. In the present study as well the incidences of Rh- blood type in mothers were higher in all NTD groups (21% for T, 22% for LS, and 19% for OE) although the difference was not significant.

When the data from the present study were partitioned by parity, it was found that the incidence of Rh- mothers decreased with parity, although not significantly so. This is in contradiction to the observation by Golding and Butler[87], who had proposed that Rh isoimmunization may be etiologically significant. The present study noted that the incidence of Rh incompatibility among parents of index cases was not increased over the incidence among controls. If Rh antibodies were involved in causing NTD, then an excess of Rh incompatibility should be observed. The incidence of Rh incompatibility was lower than expected.

Secondly, if Rh isoimmunization were an important factor, then a primaparity effect which was been found reasonably consistently in other studies should not be noted. It seems that the Rh- blood type may be related in some other, more obscure fashion than by isoimmunization.

FEBRILE ILLNESS

Overall, 19.0% of index mothers reported having a febrile illness during the first two months of pregnancy. Previous studies examining the percentage of mothers having febrile illness during pregnancy have not used the same criteria. Miller et al.[98] found that 11% of mothers of anencephalics reported hyperthermic episodes at or near the time of anterior neuropore closure. Chance et al.[99] found that 3/43 (6.98%) of mothers having spina bifida affected infants (level L-5 or higher) reported hyperthermic episodes at or near the time of posterior neuropore closure. In a prospective study, Coffey et al.[96] found that 74% of mothers having children with NTD reported having influenza during pregnancy (34% during the first trimester). The present data are still not inconsistent with their findings. Although Kleinebrecht et al.[97] did not find a significant difference for influenza or febrile illness during the first twelve weeks, it is possible that their time frame was too large. Their data showed that the incidence of NTD among mothers having influenza was .9% and .7% among mothers having febrile illness as compared to .5% and .4% of controls. This finding is not significantly different from Coffey's incidence of 1.2% of NTD among mothers having influenza ($X^2 = 1.21$).

Whereas it is apparent that hyperthermia may be significant in the etiology of some NTD, it appears that it is only important in causing LS and T type defects. Since LS

and T defects are consistent with neural tube non-closure, it is possible that hyperthermia interferes with mid-line closure rather than neural tube rupture. The finding that hyperthermia in the tenth week of pregnancy is related to clefting supports the hypothesis that hyperthermia affects mid-line closure processes.

ORAL CONTRACEPTIVES

19.9% of index mothers reported oral contraceptive usage within three months of conception as compared to 11.1% of controls. When partitioned by level, it was found that usage was reported by 19.4% of T mothers, 21.1% of LS mothers, and 13.6% of OE mothers. Significantly more mothers of probands with LS defects reported using oral contraceptives within three months of conception or during pregnancy as compared to normal sibs. None of the other comparisons were significant. This data supports the prospective findings of Kasan _et al_.[106] which showed that women who took oral contraceptives within three months of conception were more than twice as likely to have a child with a NTD. It is especially noteworthy that when the encephaloceles and iniencephalics were considered separately, there was no significant difference in incidence of these defects, while the incidence of anencephaly and spina bifida affected infants remained elevated with a X^2 value of 9.8. Together with the present study, it suggests that oral contraceptive usage within three months of conception may influence the risk of having

a child with a NTD of a certain type.

Since the usage of oral contraceptives at most triples the risk of NTD, it is likely that oral contraceptives are peripherally, but not directly, involved. The could possibly alter the vitamin and mineral levels in susceptible individuals, which in turn would disrupt neural tube closure.

ANTI-EMETICS

Overall, 29.8% of mothers of NTD probands reported anti-emetic ingestion during pregnancy. However, only mothers of OE and T probands reported ingestion of anti-emetics more often than did control mothers. Although mothers of the T group also reported taking anti-emetics more often than did mothers of the LS group, the difference was not significant. Whereas the LS vs. sib comparison was significant, the T vs. sib and OE vs. sib comparisons were not. Comparisons revealed that mothers of OE and T groups took anti-emetics more often during all pregnancies than did LS mothers.

The OE vs. LS proband comparison supports the findings by Cordero *et al.*[117], who had found that anti-emetic usage was significant for encephaloceles, but not for other NTD. However, the observation that OE and T mothers took anti-emetics more often in all pregnancies makes the conclusion tenuous. It is impossible to discern whether the cause of hyperemesis, hormone fluctuation, or the result of hyperemesis, mineral imbalances, is significant. It is also difficult to discern whether the mechanism is the same for both

OE and T defects. However, it is possible to state that since Cordero found that the incidence of encephaloceles was only doubled, anti-emetics are unlikely to be teratogens which directly affect neural tube formation, but rather are peripherally involved by reflecting another process or processes which are more closely related.

HORMONE USAGE

Significantly more mothers reported ingesting hormone preparations during pregnancy than did LS or control mothers. There is a paucity of research done on whether hormones play a role in NTD etiology. The only studies encountered in the literature were by Greenberg et al.[103], who examined the hormonal pregnancy tests; and Ahlgren et al.[125] who noted that clomiphene may be a significant factor. Neither study clearly indicated hormones as important causative factors in NTD, although mothers of the index groups had a higher incidence of usage as compared to controls in each study. The present study suggests that hormones are significant only for OE type defects.

Since OE type defects make up a small percentage of all NTD, it is not surprising that other studies have not identified definitive relationships between hormones and NTD. It should be noted that since a strong relationship was not found in the present study, it seems likely that hormones in themselves are not teratogens, but rather reflect an underlying process such as hormonal imbalance.

GYNECOLOGICAL PROBLEMS

Overall, 9.3% of the index mothers reported gynecological problems as compared to 4.8% of controls. Only mothers of the OE group significantly more often reported gynecological problems, including infertility, anovulation, highly irregular periods, or hypothyroidism. Ahlgren[125] noted that women prone to having NTD children were subfertile; while others believe that mothers of NTD affected children are more fertile, based on their observation that dizygous twinning rates and anencephaly rates are positively correlated. Wynne-Davies[39] reported that half of the mothers of spina bifida children reported gynecological problems, including irregular periods, infertility, or other menstrual disorders, as compared to less than one quarter of controls. Although the numbers are different in her study and the present study, the proportions are the same. This implies that mothers who have children with certain NTD are also more likely to have gynecological problems that are hormonally caused. This is consistent with the previous hypothesis regarding the use of anti-emetics and hormones and OE type defects. This also implies that hormonal imbalances may be significant in causing neural tube rupture, but not neural tube non-closure.

IPG AND ABORTION PRECEDING CONCEPTION

A short IPG and occurrence of conception following an abortion are significant factors in the OE group. These

support the fetus-interaction theory proposed by Knox[118]. This theory states that NTD are the result of unfavorable interaction between residual trophoblast from a miscarriage and a subsequent pregnancy. Support for this theory comes from the findings of Gardiner et al.[129], who described an increased incidence of malformations in pregnancies following an abortion, as compared to pregnancies following viable births. They also found that the IPG tended to be shorter for the index cases, especially where the result of the pregnancy was a NTD. However, the authors did not mention if a specific type of NTD was noted.

Record et al.[76] noted a shorter IPG preceding the birth of a proband with a NTD as compared to controls (29.9% vs. 33.6%), although they did not comment on the significance. When separated by type of NTD, they found that the shortest mean IPG was for the spina bifida group (25.9), followed by anencephalics (30.4) and hydrocephalics (37.3).

It was possible to examine the data of Williamson[31], Carter et al.[28], and Nevin et al.[74] regarding the abortion rate (see Table 86). When their data were pooled, 14.9% of spina bifida probands followed an abortion as compared to 9.8% of anencephalics, which was significant at the .05 level ($X^2 = 6.481$). In the present study, 19.2% of all NTD probands followed an abortion as compared to 14.3% of controls. Only the OE group was significant in having a shorter IPG or following an abortion when compared to the

TABLE 86

PROPORTION OF PREGNANCIES PRECEDED BY AN ABORTION

Reference	Defect in proband: A		SB	
	yes	no	yes	no
31	9	59	4	24
28	60	363	24	337
74	24	110	19	73
Total	93	532	47	434

other groups or controls. When the present data were compared to the data of Williamson, Carter and Nevin, the T and LS groups were not significantly different (X^2 = 1.919 and .243 respectively), whereas the OE comparison was significant at the .001 level (X^2 = 12.652). It is unfortunate that the appendix in the Carter et al.[43] study which listed encephaloceles separately did not give information on miscarriages in the sibship.

The implication from these findings are that whereas NTD individuals are more likely as a whole to follow an abortion and to have a shorter IPG, that tendency is more prominent in the OE group.

SUMMARY

The present study has attempted to show that differences in either epidemiological or etiological factors exist when NTD are divided according to level of the defect. In general, the significant factors for the OE group were hormonal or maternal in that siblings were aborted more frequently, hormone ingestion was reported more often during pregnancy, the mothers more often had hormonal gynecological problems, the inter-pregnancy gap tended to be shorter, and the conception of the affected individual occurred after an abortion more often. For the LS and T groups, significant factors included febrile illness and oral contraceptive use within three months of conception. The ABO blood type distribution was also significant in the LS group and the O group.

The significant differences which reflect heterogeneity (intra-group comparisons) are as follows:

	elevated in
T vs. LS	
1. Abortion incidence of sibships	T
T vs. OE	
1. Shortened IPG	OE
2. Febrile illness	T

LS vs. OE — elevated in

1.	Abortion incidence in sibships	OE
2.	Anti-emetic usage	OE
3.	Maternal hormonal usage	OE
4.	Shortened IPG	OE
5.	Conception after abortion frequency	OE

Differences which reflect significant etiological factors were found by doing inter-group comparisons. These were as follows:

T vs. control

1.	Febrile illness	T
2.	Anti-emetic usage	T

LS vs. control

1.	Febrile illness during first two months	LS
2.	Blood type B frequency	LS
3.	Blood type A frequency	control
4.	Incidence of pyloric stenosis in relatives	controls

OE vs. control

1.	Incidence of abortions in sibships	OE
2.	Anti-emetic usage	OE
3.	Hormone usage	OE
4.	Gynecological problems	OE
5.	Shortened IPG	OE
6.	Conception after abortion frequency	OE

T vs. siblings

1.	Febrile illness during first two months	T

LS vs. siblings

1.	Febrile illness	LS
2.	Anti-emetic usage	LS
3.	Oral contraceptive usage	LS

OE vs. siblings	elevated in
1. Hormone usage	OE
2. Shortened IPG	OE
3. Conception post ab	OE

Another accomplishment of the study was to demonstrate that clefting and hydrocephalus are more frequent among the siblings of NTD probands, when the data from the literature survey were pooled.

In conclusion, this study has demonstrated that heterogeneity apparently exists between different levels of NTD. One basis for the heterogeneity could be based on embryological occurrences such that T and LS type defects could be caused by neural tube non-closure whereas OE type defects could be the result of neural tube rupture. This would explain not only the heterogeneity observed in this study, but the inconsistencies between previous studies. Hopefully new avenues of research have been suggested for the future.

APPENDIX A

FAMILY HISTORY

KEY TO ABBREVIATIONS AND SYMBOLS USED IN APPENDICES OF FAMILY HISTORY

Abbreviations:

ASB = Anencephaly and/or Spina Bifida

CHD = Congenital Heart Defect

PS = Pyloric Stenosis

CF = Clubfoot

CLP = Cleft Lip/Palate

Symbols:

= number

o = degree relative

0 = negative history

+ = positive history

- = not available or unknown

FAMILY HISTORY

GROUP: Thoracic - Michigan Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:													
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	8	10	39	0		0		0		0		0		0		0	
2	3	10	42	0		0		0		0		0		0		0	
																1	
3	5	10	37	1	1	0		0		0		0		0		4	1
																1	3
4	4	20	65	1	4	0		0		0		1	2	0		1	1
5	3	5	23	0		0		0		0		0		0		4	2
6	3	7	19	0		0		0		0		0		0		1	2
7	4	9	20	0		0		0		1	2	0		0		2	1
																1	2
8	3	11	17	0		0		0		0		0		0		0	
9	5	8	32	0		0		0		0		0		0		0	
10	4	8	29	2	5	0		0		0		0		0		0	
11	4	6	31	0		0		0		0		0		0		0	
12	4	13	37	0		0		0		0		0		1	3	2	3

FAMILY HISTORY

GROUP: Thoracic - U. S. Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY AMONG 1ST, 2ND, 3RD DEGREE RELATIVES													
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	2	8	17	0		0		1	3	0		0		0		0	
2	2	8	20	0		0		0		0		0		0		4	1
3	2	6	18	0		0		0		0		0		0		0	0
4	4	6	26	0		0		0		0		0		0		0	0
5	2	15	21	0		0		0		0		0		0		1	1
6	2	12	31	0		0		0		0		0		0		0	
7	2	12	47	0		0		1	2	0		0		0		1	3
8	2	9	33	0		0		0		0		0		0		1	2
9	4	16	59	0		0		0		0		0		0		0	
10	3	8	24	0		0		0		0		0		0		2	2
																1	3
11	4	8	33	0		0		0		0		0		0		0	
12	2	15	63	1	7	0		0		0		0		0		1	2
																2	2
13	2	4	20	0		0		0		0		0		0		0	
14	2	8	25	0		0		0		0		0		0		0	
15	3	4	19	0		0		0		0		0		0		0	
16	2	-	-	0		0		0		0		3	3	1	3	1	3
17	4	5	23	0		0		0		0		0		0		2	1
18	3	9	24	0		0		0		0		0		0		2	1
19	4	18	48	0		0		0		0		0		0		1	1

FAMILY HISTORY

GROUP: Lumbar - Michigan Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	3	9	28	0		0		1	3	0		0		0		2	1
2	2	8	33	0		0		0		0		0		0		0	
3	4	6	19	0		0		0		0		0		0		0	
4	3	13	43	0		0		0		0		0		0		0	
5	7	19	83	0		0		0		0		0		0		1	1
6	3	9	41	0		0		0		0		0		0		0	
7	4	10	26	0		0		0		0		0		0		0	
8	5	4	37	0		0		0		0		0		0		5	2
9	2	8	19	0		0		0		0		0		0		0	
10	4	9	34	0		0		0		0		0		0		0	
11	4	12	25	0		0		0		0		0		0		1	1
12	2	8	31	0		0		0		0		0		0		2	1
13	4	10	39	0		0		0		0		0		0		0	
14	3	11	38	0		0		0		1	1	0		0		0	
15	2	7	29	0		0		0		0		0		0		1	
																3	2
16	3	10	14	0		0		0		1	1	0		0		0	
17	5	11	23	0		0		1	2	0		0		0		1	1
																1	2
18	2	12	17	0		0		0		0		0		0		2	3
19	3	10	27	1	6	0		0		0		0		0		1	2
20	4	16	63	1	4	0		0		0		0		0		0	

FAMILY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	NUMBER OF RELATIVES FIRST	SECOND	THIRD	FAMILY HISTORY OF: ASB #	ASB o	HYDROCEPHALUS #	HYDROCEPHALUS o	CHD #	CHD o	PS #	PS o	CF #	CF o	CLP #	CLP o	MISCARRIAGE #	MISCARRIAGE o
21	4	8	19	0		0		0		0		0		0		1	2
22	3	9	21	2	9	0		0		0		0		0		1	2
23	2	11	39	0		0		0		0		1	3	0		0	
24	5	10	46	0		0		0		0		0		0		0	
25	4	7	8	0		0		0		0		0		0		0	
26	4	11	12	2	2	0		0		0		0		0		2	1
27	4	8	31	0		1	4	1	2	0		0		0		1	1
								3	3							2	3
28	5	8	23	1	3	0		0		0		0		0		0	
29	3	6	21	0		0		0		0		0		0		2	2
30	3	14	40	0		0		0		0		0		0		1	1
																2	3
31	3	13	42	0		0		1	3	0		0		0		1	3
32	5	7	30	0		0		0		0		0		0		1	1
33	2	13	38	0		0		0		0		0		0		0	
34	4	8	21	0		0		0		0		0		0		0	
35	4	23	50	0		0		0		0		0		0		0	
36	3	5	22	0		1	7	0		0		0		0		1	1
37	5	10	49	0		0		1	1	0		0		0		1	1
38	4	13	45	0		0		0		0		3	3	0		1	1
																3	2
39	2	11	33	1	7	0		0		0		0		1	3	2	3
				1	8												

FAMILY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:													
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
40	5	12	44	0		0		0		0		0		0		0	
41	3	13	50	0		0		0		0		0		0		0	
42	8	16	55	0		0		0		0		1	2	0		1	1
43	3	8	14	0		0		0		0		0		0		0	
44	2	12	46	1	2	0		0		0		0		0		2	2
45	4	8	24	1	5	0		0		0		0		0		1	2
				1	6												
46	5	8	32	1	7	0		0		0		0		0		0	
47	3	10	48	0		0		0		0		0		0		0	
48	5	16	23	1	5	0		0		0		0		0		1	1
																1	2
49	7	15	58	0		0		1	1	0		0		0		0	
50	9	10	16	0		0		0		0		0		0		3	1

FAMILY HISTORY

GROUP: Lumbar - U.S. Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	4	13	21	0		1	3	0		0		0		0		0	
2	4	11	36			0		0		0		0		0		2	2
3	3	11	33	0		1	2	0		0		0		0		0	
4	3	7	19	0		0		0		0		0		0		1	1
5	2	9	20	0		0		0		0		0		0		0	
6	3	5	30	0		0		0		0		0		0		1	1
																1	2
7	2	11	11	1	4	0		0		0		0		0		2	1
																1	2
8	2	11	29	1	7	0		0		0		0		0		1	3
				1	10												
9	3	8	21	0		0		0		0		0		0		1	1
10	5	10	32	0		0		0		0		0		0		1	2
11	4	8	15	0		0		0		0		0		0		3	2
12	2	10	32	0		0		0		0		0		0		0	
13	5	9	53	1	4	0		0		0		2	2	0		0	
14	2	14	41	1	5	0		0		0		0		0		0	
15	3	10	22	0		0		0		0		1	3	0		1	3
16	4	9	19	0		0		0		0		0		0		0	
17	3	6	26			0		0		0		0		0		0	
18	3	7	17	0		0		0		0		0		0		0	
19	2	16	88	0		0		0		0		0		0		0	
20	2	26	61	1	7	0		0		0		0		0		0	

GROUP: Lumbar - U.S. Data (con't)

PT. #	NUMBER OF RELATIVES FIRST	SECOND	THIRD	FAMILY HISTORY OF: ASB #	ASB o	HYDROCEPHALUS #	HYDROCEPHALUS o	CHD #	CHD o	PS #	PS o	CF #	CF o	CLP #	CLP o	MISCARRIAGE #	MISCARRIAGE o
21	3	9	26	1	3	1	3	0		0		0		0		1	2
22	3	12	42	0		0		0		0		0		0		0	
23	3	10	34	0		0		0		0		0		0		0	
24	2	9	21	1	2	0		0		0		0		0		1	1
				1	3												
25	4	8	26	0		0		0		0		0		0		1	1
26	4	13	37	0		0				0		0		0		1	1
27	3	11	43	0		0		0		0		0		0		0	
28	5	13	38	0		0		0		0		0		0		2	3
29	3	11	42	1	5	0		0		0		0		0		0	
30	2	9	19	0		0		0		0		0		0		0	
31	2	13	42	0		0		0		0		0		0		0	
32	3	9	13	0		0		0		0		0		0		0	
33	3	8	17	0		0		0		0		0		0		1	1
34	3	9	35	0		0		1	3	0		1	3	0		1	1
35	2	4	15	1	4	0		0		0		0		0		0	
36	2	8	50	0		0		0		0		0		0		3	1
37	2	8	33	0		0		0		0		0	•	1	3	0	
38	3	5	8	0		0		0		0		0		0		0	
39	2	14	37	0		0		0		0		0		0		0	
40	3	8	23	0		0		0		0		0		0		0	
41	5	6	14	0		0		0		0		0		0		1	1
																1	2

FAMILY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
42	4	8	27	0		0		0		0		0		0		0	
43	4	8	46	0		0		0		0		0		0		0	
44	3	12	26	0		0		0		0		0		0		0	
45	4	8	38	0		0		0		0		0		0		0	
46	2	6	21	0		0		0		0		0		0		1	2
47	4	7	27	0		0		0		0		0		0		1	1
48	2	9	54	1	4	0		0		0		0		0		2	2
49	4	12	8	0		0		0		0		0		0		0	
50	4	11	41	0		0		0		0		0		0		1	2
51	3	8	34	0		0		0		0		0		0		0	
52	4	4	27	0		0		1	2	0		0		0		1	1
53	3	8	26	0		0		0		0		0		0		1	1
54	3	8	25	0		0		0		0		0		0		3	3

FAMILY HISTORY

GROUP: Sacral - Michigan Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	2	4	15	0		0		0		0		0		0		1	1
2	3	5	8	1	1	0		0		0		0		0		0	
3	4	12	62	0		0		0		0		0		0		0	
4	3	8	24	0		0		0		0		0		0		1	1
5	2	13	32	0		0		0		0		0		0		0	
6	4	8	20	1	1	0		0		0		1	3	0		1	1
7	4	8	29	0		0		0		0		0		0		0	

FAMILY HISTORY

GROUP: Sacral - U.S. Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	4	6	21	0		0		0		0		0		0		0	
2	3	18	56	0		0		0		0		0		0		0	
3	4	9	37	0		0		0		0		0		0		0	
4	3	7	27	1	3	0		0		0		0		0		0	
5	4	10	30	0		0		0		0		0		0		0	
6	2	7	21	1	5	0		0		0		0		0		1	2
																6	3
7	2	10	19	0		0				0		0		0		0	
8	2	12	38	0		0		0		0		0		0		0	
9	3	7	24	0		0		0		0		0		0		0	
10	2	10	39	0		0		0		0		0		0		0	
11	2	7	31	1	5	0		0		0		0		0		0	
12	3	11	42	0		0		0		0		0		0		0	
13	3	9	16	1	3	0		1	3	0		0		0		0	
14	7	19	102	1	4	0		0		0		1	2	0		1	1
												1	3				
15	3	10	21	0		0		0		0		0		0		0	

FAMILY HISTORY

GROUP: Other - Michigan Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	5	8	34	0		0		0		0		0		0		1	1
2	2	6	26	0		0		0		0		0		0		0	
3	4	7	24	0		0		0		0		0		0		1	2
4	4	-	-	1	4	0		0		0		0		0		0	
5	2	12	22	0		0		0		0		0		0		1	3
6	2	15	35	0		0		0		0		1	3	0		0	
7	6	8	25	0		1	4	0		0		0		0		1	1
8	3	6	7	0		0		0		0		0		0		2	1
9	3	14	36	1	2	0		0		0		0		0		3	1
10	3	6	19	0		0		0		0		0		0		1	1
11	2	9	31	0		0		1	3	0		1	3	1	3	2	1
																3	3

FAMILY HISTORY

GROUP: Other - U.S. Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	4	15	46	0		0		1	3	0		0		1	3	1	1
																2	3
2	6	9	62			0		0		0		0		0		1	1
3	4	4	31	0		0		0		0		0		0		1	2
4	5	8	20	0		0		1	2	0		0		0		4	1

FAMILY HISTORY

GROUP: Encephalocele - Michigan Data

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	3	7	24	0		0		0		0		0		0		2	1
																4	2
																6	3
2	2	6	30	0		0		0		0		0		0		0	
3	7	9	21	0		0		0		0		0		0		5	1
4	3	8	30	0		0		0		0		0		0		1	1
																3	2
5	2	11	17	0		0		0		0		0		0		1	2
																1	3
6	5	7	32	0		0		0		0		0		0		1	1
																2	2
7	7	12	32	0		1	3	1	3	0		0		0		0	

FAMILY HISTORY

GROUP: Control

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
1	2	7	15	0		0		0		0		0		0		1	1
2	4	11	31	0		0		0		0		1	2	0		1	1
																4	2
3	3	8	32	0		0		0		0		0		0		1	1
4	2	4	17	0		0		0		0		0		0		1	1
5	3	10	29	0		0		0		0		0		0		1	1
6	3	9	39	0		0		0		0		0		0		1	2
7	3	20	37	0		0		0		0		0		0		0	
8	3	11	63	0		0		0		0		0		0		1	2
																1	3
9	6	15	39	0		0		0		0		0		0		0	
10	2	7	21	0		0		0		0		0		0		0	
11	3	7	19	0		0		0		0		0		0		1	1
																1	2
12	2	17	36	0		0		0		0		0		0		0	
13	2	13	33	0		0		1	3	0		0		0		0	
14	4	10	34	0		0		0		0		0		0		0	
15	3	5	20	0		0		0		0		0		0		0	
16	2	6	29	0		0		0		0		0		0		1	2
17	3	11	24	0		0		0		0		0		0		1	1
18	6	6	43	0		0		1	2	0		0		0		3	2
19	4	14	50	0		0		0		0		0		0		1	1
20	3	9	20	0		0		0		0		0		0		0	

FAMILY HISTORY

GROUP: Control (con't)

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
21	5	13	39	1	2	0		0		0		0		0		0	
22	3	10	36	0		0		0		0		0		0		0	
23	5	8	40	0		0		0		0		0		0		1	2
24	3	6	21	0		0		0		0		0		0		2	1
25	4	4	13	0		0		0		0		0		0		1	1
26	4	13	73	0		0		0		0		0		0		1	1
27	4	6	20	0		0		0		0		0		0		0	
28	4	7	8	0		0		0		0		0		0		2	1
29	5	15	50	0		0		0		0		0		0		0	
30	4	7	20	0		0		0		0		0		0		0	
31	3	6	20	0		0		0		0		0		0		0	
32	4	13	55	1	2	0		0		0		0		0		0	
33	2	10	41	0		0				0		0		0		0	
34	5	8	26	0		0				0		0		0		1	1
35	3	11	25	0		0		0		0		0		0		1	1
																1	2
36	3	13	51	0		0		0		0		0		0		0	
37	3	6	13	0		0		0		0		0		0		0	
38	6	5	17	0		0		0		0		0		0		2	1
39	4	10	18	0		0		0		0		0		0		0	
40	2	17	26	0		0		0		0		0		0		3	1
41	4	9	46	1	4	0		0		0		0		0		0	
42	4	11	-	0		0		0		0		0		0		0	

FAMILY HISTORY

GROUP: Control (con't)

PT. #	NUMBER OF RELATIVES			FAMILY HISTORY OF:											
	FIRST	SECOND	THIRD	ASB		HYDROCEPHALUS		CHD		PS		CF		CLP		MISCARRIAGE	
				#	o	#	o	#	o	#	o	#	o	#	o	#	o
43	5	10	35	0		0		0		0		0		0		0	
44	3	7	26	0		0		0		0		1	4	0		1	1
																1	2
																1	3
45	2	9	22	0		1	3	0		0		0		0		0	
46	3	9	25	0		0		-		-		-		-		-	
47	4	7	40	0		0		1	3	0		0		0		0	
48	7	13	21	1	3	0		0		0		1	1	0		1	1
49	2	13	21	0		0		0		0		0		0		1	2
50	3	7	41	0		0		0		0		0		0		0	
51	4	11	71	0		0		0		0		0		0		0	
52	2	7	16	0		0		0		0		0		0		0	
53	5	13	73	0		0		0		0		0		0		1	3
54	3	10	41	0		0		0		0		1	3	1	4	0	
55	2	9	25	0		0		0		0		0		0		0	
56	2	7	17	0		0		0		0		0		0		0	
57	3	9	22	0		0		0		0		0		0		0	
58	6	9	40	1	3	0		0		0		0		0		1	3
59	4	16	43	0		0		2	2	0		0		0		0	
								2	3								

APPENDIX B

PREGNANCY HISTORY

KEY TO ABBREVIATIONS AND SYMBOLS USED IN APPENDICES OF PREGNANCY HISTORY

Abbreviations:

* = proband
ab = abortion
B.D. = birth date (month-year)
OC = oral contraceptive usage
time = time of infection
Anti-em. = anti-emetic usage
other = other medications

Symbols:

# = number
o = degree relative
0 = negative history
+ = positive history
- = not available or unknown

PREGNANCY HISTORY

GROUP: Thoracic - Michigan Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	8-	0	0	0	0	0	0	-
	M	2	2-	1	0	0	0	0	0	9
1	F	3	11-	0	0	0	0	0	0	0
	M	4	10-	0	0	0	0	0	0	26
	M	5	11-	0	0	0	0	0	0	40
	F	6	10-	0	0	0	0	0	0	26
	*F	7	7-	0	0	0	0	0	0	48
	ab	1		+	0	0	0	0	0	-
2	*M	2	6-	0	0	+ 2nd m.	0	0	0	12
	-	3	10-80	0	0	0	0	0	0	60
	ab	1		0	+	0	0	+	0	-
	ab	2		0	+	0	0	+	0	12
	F	3		0	+	0	0	+	0	6
3	F	4		0	+	0	0	+	0	24
	F	5		0	+	0	0	+	0	19
	ab	6		0	+	0	0	+	0	8
	ab	7		0	+	0	0	+	0	20
	*F	8		0	0	0	0	+	0	110
	ab	1		0	0	0	+	0	0	-
4	F	2	1-	0	0	0	+	0	0	6
	F	3	2-	0	0	0	+	0	0	16
	*M	4	7-	+	0	+ 1st m.	+ 1st m.	0	+	20

PREGNANCY HISTORY

GROUP: Thoracic - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
5	*F	1	5-	+	0	0	0	+	+	-
	-	2		0	0	0	0	0	0	4
6	F	1	3-	0	0	0	0	0	0	-
	*F	2	2-	+	0	0	0	+	0	51
	ab	1	-	0	0	0	0	0	0	-
	M	2	7-	0	0	0	0	0	0	12
7	F	3	8-	0	0	0	0	0	0	15
	ab	4	-	0	0	0	0	0	0	52
	*F	5	1-	+	0	0	0	0	+	60
8	M	1	8-	0	0	0	0	+	0	-
	*M	2	10-	0	0	0	0	0	0	22
	-	1	1-	0	0	0	0	0	0	-
9	*F	2	7-	0	0	+ 5 wks.	0	0	0	21
	-	3	3-	0	0	0	0	0	0	11
	-	4	3-	0	0	0	0	0	0	15
	F	1	10-	0	0	0	0	0	0	-
10	F	2	6-	0	0	0	0	0	0	11
	*F	3	8-	0	0	+ 1-2 m.	0	0	0	77

PREGNANCY HISTORY

GROUP: Thoracic - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	*M	1	12-	0	0	+ time unk.	0	0	+	-
11	-	2	3-	0	0	0	0	0	0	6
	-	3	8-	0	0	0	0	0	0	30
	-	1		0	0	0	0	+	0	-
12	*F	2		0	0	+ 1-5 m.	0	+	0	-
	-	3		0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Thoracic - U.S. Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
1	*F	1	1-	0	0	0	0	+	0	-
	*M	1	11-73	0	0	+ 2 m.	0	0	0	-
	ab	2		0	0	0	0	0	0	-
2	ab	3		0	0	0	0	0	0	-
	ab	4		0	0	0	0	0	0	-
	ab	5		0	0	0	0	0	0	-
3	*F	1		+	0	0	0	0	+	-
	M	1	3-64	0	0	0	0	0	0	-
4	M	2	5-68	0	0	0	0	0	+	41
	*F	3	11-70	0	0	0	0	0	+	21
5	ab	1	1-79	0	0	+ 2 m.	0	+	0	-
	*M	2	7-79	0	+	0	0	+	0	3
6	*M	1	10-79	0	0	0	0	0	0	-
7	*-	1	9-76	0	0	0	+ 3 wks.	+	0	-
8	*M	1	8-75	0	0	0	+ time unk.	0	+	-

PREGNANCY HISTORY

GROUP: Thoracic - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	*F	1	4-69	0	0	0	0	0	+	-
9	F	2	7-70	0	0	0	0	0	0	6
	F	3	10-71	0	0	0	0	0	0	6
10	F	1	6-77	0	0	0	0	+	0	-
	*F	2	6-80	0	0	+ 5-8 m.	+ strep throat	+	+	27
	F	1	6-69	0	0	0	0	+	0	-
11	F	2	6-74	0	0	0	0	+	0	51
	*M	3	9-78	0	0	+ 4 wks.	0	+	+	42
12	ab	1	5-77	0	0	+ 2-3 m.	0	0	0	-
	*F	2	5-79	0	+	+ 5 m.	+ 5 wks. cold	+ 5 m.	+	20
13	*F	1	9-74	0	0	0	0	0	0	-
14	*-	1		0	0	0	0	+	0	-
15	M	1	2-71	+	0	0	0	0	0	-
	*F	2	9-74	+	+ spotting	0	0	0	0	34
16	*M	1	9-74	0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Thoracic - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	ab	1		0	0	0	0	0	0	-
	*F	2	6-71	0	0	0	+ 2nd m.	0	+	-
17	ab	3		0	0	0	0	0	0	-
	-	4	4-75	0	0	0	0	0	0	-
	-	5	4-80	0	0	0	+ 5 m. throat	0	+	51
	ab	1	-63	0	0	0	0	0	0	-
18	F	2	12-64	0	0	0	0	0	0	-
	ab	3	-65	0	0	0	0	0	0	-
	*M	4	-68	0	0	0	0	+	0	28
	ab	1	-67	0	0	0	0	+	0	-
19	*F	2	2-71	0	0	0	0	+	0	20
	F	3	8-76	0	0	0	0	+	0	57
	M	4	11-79	0	0	0	0	+	0	30

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	ab	1	9-	0	0	0	0	0	0	-
1	ab	2	5-	0	0	0	0	0	0	8
	M	3	5-	0	0	0	0	0	0	25
	*F	4	11-	+	+	0	0	0	0	21
2	*F	1	11-	0	0	0	0	0	0	-
	*F	1	8-	0	0	0	0	0	0	-
3	-	2	5-	0	0	0	0	0	0	18
	-	3	9-	0	0	0	0	0	0	43
4	*M	1	2-	0	0	0	0	+	0	-
	M	2	8-	0	0	0	0	+	0	3
	F	1	8-	0	0	0	0	0	0	-
	F	2	8-	0	0	0	0	0	0	15
	M	3	2-	0	0	0	0	0	0	14
5	F	4	11-	0	0	0	0	0	0	19
	ab	5	-	0	0	0	0	0	0	36
	M	6	2-	0	0	0	0	0	0	14
	*F	7	12-	0	0	0	0	0	0	13
6	*M	1	1-	0	0	0	0	0	0	-
	F	2	7-	0	0	0	0	0	0	11

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	M	1	7-	0	0	0	0	0	0	-
7	M	2	7-	+	0	0	0	0	0	27
	*F	3	4-	+	0	0	0	0	+	51
	F	1	3-	0	0	0	0	0	+	-
8	M	2	5-	0	0	0	0	0	+	17
	F	3	8-	0	0	0	0	+	+	6
	*M	4	1-	+	0	0	0	+	+	32
9	*M	1	8-	+	0	0	0	0	0	0
10	M	1		0	0	0	0	0	0	-
	*M	2	2-	0	0	0	0	0	0	100
	*F	1	11-	0	+	0	0	0	0	-
11	F	2	12-	0	+	0	0	0	0	40
	F	3	12-	0	+	0	0	0	0	3
	ab	1		0	0	0	0	0	0	-
12	ab	2		0	0	0	0	0	0	24
	*F	3	4-	0	0	0	0	0	+	6
13	M	1	9-	0	0	0	0	0	0	-
	F-F*	2	2-	0	0	0	0	+	0	48

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
14	*F	1	4-	0	0	0	0	0	0	-
	M	2	4-	0	0	0	0	0	0	75
15	*F	1	3-	0	0	0	0	0	0	-
16	F-F*	1	6-	0	0	0	0	0	0	-
	-	1		0	0	0	0	0	0	-
	-	2		0	0	0	0	0	0	-
17	-	3		0	0	0	0	0	0	-
	-	4		0	0	0	0	0	0	-
	*F	5		0	0	0	0	0	0	-
18	*F	1		0	0	+ time unk.	0	0	0	-
19	*F	1	1-	+	0	0	0	0	0	-
	M	2	11-	+	0	0	0	0	0	11
	M	1	11-	0	0	0	0	0	0	-
20	F	2	6-	0	0	0	0	0	0	33
	*M	3	1-	0	0	0	0	0	0	22
	F	1	4-	0	0	0	0	0	0	-
21	-	2	9-	0	0	+	0	0	0	32
	*M	3	11-	0	0	+ 1st m.	0	+	0	17

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
22	*M	1	2-	0	0	0	+ cold 4 wks.	+	0	-
	F	2	12-	0	0	0	0	0	0	13
23	*M	1	2-	0	0	0	0	0	0	0
	M	1	6-	0	0	0	0	0	0	-
24	*F	2	7-	0	0	+ 8 wks.	0	0	0	4
	M	3	10-	0	0	0	0	0	0	6
	M	4	11-	0	0	0	0	0	0	4
	M	1	6-	0	0	0	0	0	0	-
25	F	2	4-	0	0	0	0	0	0	73
	*F	3	9-	0	0	+ 2 m.	0	0	0	80
	F	1	12-	0	0	0	0	0	0	-
	ab	2		0	0	0	0	0	0	-
26	F	3	5-	0	+	0	0	0	0	18
	ab	4		0	0	0	0	0	0	48
	*F	5		0	0	0	0	0	0	6
	M	1		0	0	0	0	0	+	-
	ab	2		0	0	0	0	0	0	2
27	ab	3		0	0	0	0	0	0	2
	*M	4	5-	0	0	0	0	0	+	18
	-	5		0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	3-	+	0	0	0	0	0	-
28	*F	2	10-	+	0	0	0	0	0	10
	M	3	8-	+	0	0	0	0	0	13
	M	4	9-	+	0	0	0	0	0	16
29	*F	1	1-	0	0	0	+ cold 3 m	+	0	-
	-	2	7-	0	0	+	0	+	0	21
	F	1	5-	0	0	0	0	0	0	-
30	ab	2		0	0	0	0	0	0	5
	*M	3		+	0	0	0	0	+	-
31	M	1		0	0	+	0	0	0	-
	*F	2	9-	0	0	+ time unk.	0	0	0	-
	F	1	11-	0	0	0	0	0	0	-
	*M	2	12-	0	0	0	0	0	+	4
32	M	3	10-	0	0	0	0	0	0	13
	F	4	4-	0	0	0	0	0	0	9
	M	5	6-	0	0	0	0	0	0	29
33	*F	1	11-	+	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
34	M-M*	1	1-	0	0	0	0	+	0	-
	F	2	8-	0	0	0	0	0	0	-
	M	1	5-	0	0	0	0	0	0	-
35	M	2	11-	0	0	0	0	0	0	21
	*M	3	5-	+	0	+ 2 m.	0	+	0	9
	ab	1	1-	0	0	0	0	0	0	-
36	M	2	4-	0	0	0	0	0	0	18
	*M	3	4-	+	0	0	0	0	0	20
	ab	1		0	0	0	0	0	0	-
	F	2	1-	0	0	0	0	0	0	-
37	*M	3	4-	0	0	0	0	0	0	60
	F	4	5-	0	0	0	0	0	0	16
	*M	5	9-	0	0	0	0	0	0	123
	ab	1		0	0	0	0	0	0	-
38	F	2	12-	0	+	0	0	0	0	-
	M	3	7-	0	0	0	0	0	0	32
	*M	4	10-	0	0	+	0	0	0	25
39	*F	1		0	0	0	0	+	0	-

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	-	1	10-	0	0	0	0	0	0	-
40	-	2	12-	0	0	0	0	0	0	41
	-	3	4-	0	0	0	0	0	0	7
	*F	4	6-	+	0	+ time unk.	0	+	0	53
41	*M	1	7-	0	0	0	+ mono 6 wks.	0	0	-
	M	2	12-	0	0	0	0	0	0	8
	M	1	5-	0	0	0	0	0	0	-
	F	2	8-	0	0	0	0	0	0	6
	M	3	10-	0	0	0	0	0	0	5
42	M	4	2-	0	0	0	0	0	0	7
	ab	5	-	0	0	0	0	0	0	4
	M	6	6-	0	0	0	0	0	0	1
	*F	7	6-	0	0	0	0	0	+	27
	F	8	1-	0	0	0	0	0	0	9
43	*M	1		+	0	0	+ fever 1-2 m.	0	0	-
	M	2	11-	0	0	+	0	0	0	53
44	*M	1		0	0	+ 2 m.	0	+	0	-

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	12-	0	0	0	0	+	0	-
45	*M	2	3-	0	0	0	0	+	0	30
	M	3	4-	0	0	0	0	+	0	4
	-	1	9-	0	0	0	0	0	0	-
46	-	2	1-	0	0	0	0	0	0	19
	*F	3	8-	0	0	+ 1-2 m.	0	0	0	10
	-	4	1-	0	0	0	0	0	0	40
47	*F	1	1-	+	0	0	0	+	0	-
	-	2	12-	0	0	0	0	+	0	13
	-	1	7-	0	0	+	0	0	0	-
	-	2	9-	0	0	0	0	+	0	5
48	*M	3	11-	0	0	0	0	0	0	17
	ab	4	-	0	0	0	0	0	0	-
	*F	5	7-	0	0	0	0	0	0	11
	F	1		0	0	0	0	0	0	-
	F	2		0	0	0	0	0	0	-
49	*F	3	10-	0	0	+ 6 wks.	0	0	0	23
	F	4		0	0	0	0	0	0	-
	M	5		0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	ab	1		0	+	0	0	0	0	-
	ab	2		0	+	0	0	0	0	-
	-	3		0	+	0	0	0	0	-
	-	4		0	0	0	0	0	0	-
50	ab	5		0	0	0	0	0	0	-
	*F	6		0	0	0	0	0	0	-
	-	7		0	0	0	0	0	0	-
	-	8		0	0	0	0	0	0	-
	-	9		0	0	0	0	0	0	-
	-	10		0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	*M	1	5-65	0	0	0	0	0	0	-
1	F	2	12-66	0	0	0	0	0	0	8
	M	3	4-69	0	0	0	0	+	0	19
	-	1		0	0	0	0	0	0	-
2	*F	2	-65	0	0	0	0	0	0	-
	-	3		0	0	0	0	0	0	-
3	F	1	7-77	0	0	0	0	0	0	-
	*M	2	7-78	0	0	0	+ 4-5 wks.	0	0	3
	M	1	9-69	0	0	0	0	0	0	-
4	*F	2	12-74	0	0	0	0	0	0	54
	ab	3		0	0	0	0	0	0	30
5	*M	1	6-80	0	0	0	0	0	0	-
	ab	1		0	0	0	0	0	0	-
6	*M	2	12-67	0	0	0	0	0	0	24
	F	3	2-71	0	0	0	0	0	0	29
	ab	1		0	0	0	0	0	0	-
7	ab	2		0	0	0	0	0	0	-
	*M	3	4-74	+	+	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU	TIME	ILLNESS	TIME	ANTI-EM.	OTHER	IPG
8	*M	1	1-78	0	0	+	1st tri.	0		0	+	-
	*M	1	11-61	0	0	+	1-6 wks.	0		0	+	-
9	ab	2	3-63	0	0	0		0		0	0	18
	M	3	3-65	0	0	0		0		0	0	15
	F	1	9-57	0	0	0		0		+	0	-
10	F	2	1-59	0	0	0		0		+	0	6
	M	3	1-62	0	0	0		0		+	0	27
	*F	4	-75	0	0	0		0		+	+	100+
	M	1	5-69	0	0	0		0		0	0	-
11	M	2	3-72	0	0	0		0		0	0	25
	*M	3	7-76	0	0	0		0		0	0	43
12	*M	1	11-79	0	0	0		0		0	0	-
	M	1	4-72	+	0	0		0		0	0	-
13	*F	2	-	+	0	0		0		+	0	-
	M	3	2-79	+	0	0		0		0	0	-
	F	4	3-80	0	0	0		0		0	0	4
14	*	1	11-79	0	0	+	time unk.	0		0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
15	*M	1	7-75	+	0	0	+ time	0	0	-
	F	2	11-72	+	0	0	0 unk.	0	0	19
	-	1	12-68	0	0	0	0	0	0	-
16	-	2	4-72	0	0	0	0	0	+	31
	*F	3	8-73	0	0	0	0	0	0	7
17	M	1	7-78	+	0	+ 5 m.	0	+	0	-
	*ab	2	11-80	0	0	+ lst tri.	0	0	0	19
	M	1	7-71	+	0	0	0	0	0	-
18	ab	2	-73	0	0	0	0	0	0	-
	*M	3	1-74	0	0	0	0	0	0	-
19	*F	1	10-70	0	0	0	0	0	0	-
20	*F	1	7-78	0	+	+ 2 m.	0	0	0	-
21	*M	1	12-76	+	0	0	0	0	0	-
	M	2	9-75	+	0	0	0	0	0	24
22	M	1	12-79	0	0	0	0	+	0	-
	*M	2	-77	0	+	0	0	+	+	24+
23	M-M*	1	4-65	+	0	0	0	+	0	-

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
24	ab	1		0	0	0	0	0	0	-
	*F	2	7-70	0	+	0	+ cold - concept.	0	+	4
	ab	1		0	0	0	0	0	0	-
25	F	2	6-68	0	0	0	0	0	0	4
	M	3	9-69	0	0	0	0	0	0	6
	*F	4		0	0	0	0	+	0	-
	M	1	7-72	0	0	0	0	0	0	-
26	F	2	8-74	0	0	0	0	0	0	16
	ab	3	-77	0	0	0	0	0	0	28
	*M	4	1-79	0	0	0	0	0	0	12
27	F	1	12-75	0	0	0	0	0	0	-
	*F	2	8-78	+	0	0	0	0	0	23
	M	1	2-55	0	0	0	0	0	0	-
28	F	2	3-56	0	0	0	0	0	0	4
	F	3	7-57	0	0	0	0	+	0	7
	*F	4	10-60	0	0	0	0	0	0	30
29	*M-F	1	2-76	0	+	0	0	0	+	-
30	*F	1	11-73	0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
31	*M	1		0	+	0	0	0	0	-
32	M	1	4-72	0	0	0	0	0	0	-
	*F	2	12-76	0	0	0	0	+	0	47
	M	1	4-77	0	0	0	0	0	0	-
33	ab	2		0	0	0	0	0	+	-
	*M	3	12-79	0	0	0	0	0	+	18
	F	1	8-74	0	+	0	0	0	0	-
34	ab	2	12-75	0	0	0	0	0	0	7
	*F	3	10-76	0	+	0	+ 3 m.	+	0	4
35	*F	1		+	0	+ time unk.	0	0	0	-
	ab	1		0	0	0	0	0	0	-
36	ab	2		0	0	0	0	0	0	-
	ab	3	-77	0	0	0	0	0	0	-
	*M	4	12-78	0	0	0	0	0	+	-
37	*F	1	-60	0	0	+ 6 wks.	0	+	0	-
38	F	1	2-72	0	0	0	0	0	0	-
	*M	2	10-75	0	0	0	0	0	0	35

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
39	*M	1		0	0	0	0	+	0	-
40	F	1	7-71	0	0	+	0	+	+	-
	*M	2	-75	0	0	+ 6 m.	0	+	+	48
	*M	1	4-70	0	0	0	0	0	0	-
41	F	2	12-76	0	0	0	+ 1 m.	0	0	71
	ab	3	10-79	0	0	0	0	0	0	25
	M-M	4	5-80	0	0	0	0	0	0	4
	M	1	11-71	0	0	0	0	0	0	-
42	F	2	6-73	+	0	0	0	0	0	10
	*F	3	-77	0	0	0	0	+	0	-
	F	1	11-55	0	0	0	0	0	0	-
43	F	2	10-60	0	0	0	0	0	0	50
	*F	3		0	0	0	0	0	0	-
44	M	1	1-77	+	0	0	+ 7 m.	0	0	-
	*M	2	5-79	0	0	+ 2 m.	0	+	+	19
	F	1	6-49	0	0	+ time unk.	0	0	0	-
45	M	2	10-50	0	0	0	0	0	+	7
	*M	3	2-58	0	0	0	0	0	_	79

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
46	*F	1	-77	0	0	0	0	0	0	-
	F	1	10-69	0	0	0	0	0	0	-
47	ab	2	-	0	0	0	0	0	0	-
	F	3	9-78	+	0	0	+ time unk.	0	0	-
	*F	4	6-80	0	0	0	0	0	+	10
48	*M	1	7-78	0	0	+ time unk.	0	0	+	-
	F	1	4-43	-	-	-	-	-	-	-
49	*F	2	8-45	-	-	-	-	-	-	19
	F	3	12-47	-	-	-	-	-	-	19
	F	1	6-67	0	0	0	0	0	0	-
50	F	2	1-70	0	+	0	0	0	0	22
	*F	3	11-73	0	0	0	+ 1 m. flu	0	0	37
51	M	1	12-77	0	0	0	0	0	0	-
	ab	1	9-69	0	0	0	0	0	0	-
52	-	2	9-74	0	0	0	+ time	0	+	51
	-	3	2-77	0	0	0	+ unk.	0	+	20
	*F	4	9-78	0	0	0	+ 1 m. cold	0	_	10

PREGNANCY HISTORY

GROUP: Lumbar - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	11-74	0	0	0	0	+	0	-
53	ab	2	7-77	0	0	0	0	0	0	23
	*M	3	6-78	0	0	+ 1-2 m.	0	+	+	8
54	M	1	11-74	0	0	0	0	+	0	-
	*M	2	6-76	+	0	0	0	+	+	10

PREGNANCY HISTORY

GROUP: Sacral - Michigan Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
1	ab			0	0	0	0	0	0	-
	*F	2		0	0	0	0	0	+	6
2	*F	1	10-	0	0	0	0	0	0	-
	*F	2	8-	0	0	0	0	0	0	18
	M	1	5-	0	0	0	0	0	0	-
3	M	2	9-	0	0	0	0	0	0	72
	*F	3	6-	0	0	0	0	0	0	130
	*M	1	6-	0	0	0	0	0	0	-
4	M	2	2-	0	0	0	0	0	0	11
	ab	3		0	0	0	0	0	0	20
5	*F	1	1-	+	+	0	0	0	0	-
	ab	1		0	0	0	0	0	0	-
6	*M	2		0	0	0	0	0	0	-
	*M	3		0	+	0	0	0	0	39
	-	4		0	0	0	0	0	0	-
	-	1	5-	+	0	0	0	0	0	-
7	-	2	6-	+	0	0	0	0	0	-
	*-	3		0	0	0	0	+	0	16

PREGNANCY HISTORY

GROUP: Sacral - U.S. Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	M	1	3-70	0	0	0	0	0	0	-
1	*M	2	-72	0	0	0	0	0	+	-
	F	3	7-74	0	0	0	0	0	0	-
2	M	1	3-78	0	0	0	0	0	0	-
	*M	2	1-80	0	0	0	0	0	0	13
	*F	1	9-69	+	0	+	0	0	0	-
3	F	2	10-70	0	0	+ 1 m.	0	0	0	2
	F	3	9-80	0	0	+	0	0	0	110
4	F	1	4-74	0	0	0	0	0	0	-
	*F	2	7-79	0	0	0	0	+	+	54
	M	1	4-65	0	0	0	0	0	0	-
5	M	2	8-66	0	0	0	0	0	0	5
	*F	3	11-70	0	0	0	0	0	0	42
6	*F	1		0	0	0	+ cold - 1-2 m.	0	+	-
	M	1	10-62	0	0	0	0	0	0	-
7	F	2	1-64	0	0	0	0	0	0	6
	M	3	5-71	+	0	0	0	+	+	79
	*F	4	-77	+	0	0	0	+	+	60+

PREGNANCY HISTORY

GROUP: Sacral - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
8	*F	1	-68	0	0	0	0	0	0	-
9	M	1	5-77	+	0	+ 5 m.	0	0	0	-
	*M	2	12-79	+	0	0	0	0	0	22
10	*F	1	2-71	0	0	+ 1 m.	0	0	0	-
11	*M	1	7-77	0	0	0	0	0	0	-
12	F	1	11-77	0	0	0	0	0	+	-
	*M	2	4-79	0	0	0	+ hot tub 1 m.	+	+	8
13	M	1	9-76	0	0	0	0	0	0	-
	*F	2	6-78	0	0	0	0	0	0	12
	F	1	12-60	0	0	0	0	0	0	-
	M	2	11-61	0	0	0	0	0	0	2
14	F	3	2-63	0	0	+ time unk.	0	0	0	11
	M	4	6-65	0	0	0	0	0	0	14
	ab	5	-65	0	0	0	0	0	0	-
	M	6	7-74	0	0	0	0	0	0	-
	*M	7	3-76	0	0	+ 2 m.	0	0	0	11

PREGNANCY HISTORY

GROUP: Sacral - U.S. Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
15	M	1	7-71	0	0	0	0	0	0	-
	*F	2	3-80	0	0	0	+ 17 wks.	0	+	71

PREGNANCY HISTORY

GROUP: Other - Michigan Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	ab	1		0	0	0	0	0	0	-
1	*F	2	7-	0	0	0	+ cold - 2 m.	+	+	1
	F	3	11-	0	0	0	0	+	+	19
	M	4	7-	0	0	0	0	0	0	11
2	*M	1		0	0	0	0	0	0	-
	M	1		0	0	0	0	0	0	-
3	F	2	2-	0	0	0	0	0	0	36
	*-	3	7-	0	0	0	0	0	0	24
	*F	1		0	+	+ early part	0	0	+	-
4	-	2		0	+	0	0	0	0	9
	-	3		0	+	0	0	0	0	36
5	*F	1	3-79	+	0	0	0	+	+	-
	M	2	3-80	0	0	0	0	0	0	3
	-	1		0	0	0	0	0	0	-
6	-	2		0	0	0	0	0	0	-
	*F	3		0	0	0	0	0	0	-

PREGNANCY HISTORY

GROUP: Other - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	*M	1	12-	0	0	0	+ bronchitis time unk.	0	0	-
7	M	2	11-	0	0	0	0	0	0	38
	ab	3	3-	0	0	0	0	0	0	12
	M	4	3-	0	0	0	0	0	0	84
	-	1		0	0	0	0	0	0	-
8	ab	2	0	+	0	0	0	0	0	-
	*-	3		0	+	0	+ 3 wks. car inf.	0	+	1
	ab	4		0	0	0	0	0	0	-
	ab	1		0	0	0	0	0	0	-
	F	2		0	0	0	0	0	0	15
9	ab	3		0	0	0	0	0	0	20
	*M	4		0	0	0	0	+	0	24
	ab	5		0	0	0	0	0	0	20
	ab	1	10-65	0	0	0	0	-	-	-
10	*F	2	10-66	0	+	0	0	+	+	3
	F	3	7-69	0	0	0	0	-	-	24
	ab	1	6-75	+	0	0	0	0	+	-
11	ab	2	8-77	0	+	0	0	0	+	17
	*F	3	3-80	+	+	0	0	+	+	22

PREGNANCY HISTORY

GROUP: Other - U.S. Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	8-69	0	0	0	0	0	0	-
1	ab	2		0	0	0	0	0	0	-
	*F	3		0	0	0	0	0	+	-
	ab	1		0	0	0	0	0	0	-
2	F	2	5-71	0	+	0	0	+	0	13
	*F	3	-75	0	+	0	0	0	+	31
	F	4	7-80	0	0	0	0	+	0	51
	F	1	9-57	0	0	0	0	0	0	-
3	*M	2	1-59	0	0	0	0	0	+	7
	M	3	4-61	0	0	0	0	0	0	18
	M	1	4-66	+	0	0	0	0	0	-
	M	2	9-67	0	0	0	0	0	0	8
	ab	3		0	0	0	0	0	0	-
4	ab	4		0	0	0	0	0	0	-
	ab	5		0	0	0	0	0	0	-
	ab	6		0	0	0	0	0	0	-
	*F	7	10-77	0	0	0	0	0	+	-

PREGNANCY HISTORY

GROUP: Encephalocele - Michigan Data

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	9-	0	0	0	0	0	0	-
1	ab	2		0	0	0	0	0	0	-
	ab	3		0	0	0	0	0	0	-
	*M	4		0	+	0	0	0	0	5
2	*F	1	9-	0	0	+ time unk.	0	0	0	-
	ab	1		0	0	0	0	+	0	-
	M	2		0	0	0	0	+	0	-
	M	3		+	0	0	0	+	0	-
	ab	4		0	0	0	0	+	0	-
3	ab	5		0	0	0	0	+	0	-
	ab	6		0	0	0	0	+	0	-
	ab	7		0	0	0	0	+	0	-
	*M	8		0	+	0	+ mumps time unk.	+	+	24
	F	9		0	0	0	0	+	0	-
	-	10		0	0	0	0	+	0	-
	*M	1	-77	+	0	0	0	+	0	-
4	ab	2	10-78	0	0	0	0	+	0	-
	M	3	3-80	0	0	0	0	+	0	17

PREGNANCY HISTORY

GROUP: Encephalocele - Michigan Data (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
5	*M	1		0	0	0	0	+	0	-
	M	1	12-76	0	0	0	+ cold -	+	0	-
6	ab	2	-79	0	0	0	+ time	0	0	24+
	*F	3	-79	0	0	0	+ unk.	+	0	1
	-	4	9-80	0	0	0	+	+	0	6
	-	1	1-44	0	0	0	0	0	0	-
7	F	2	7-45	0	0	0	0	0	0	9
	*F	3	7-46	0	0	0	0	0	+	3
	-	4	8-51	0	0	0	0	0	0	52

PREGNANCY HISTORY

GROUP: Control

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
1	ab	1	7-75	0	0	0	+ cold - time unk.	0	0	-
	*M	2	3-77	0	0	0	0	+	+	18
	*F	1	6-77	+	0	0	0	0	0	-
2	F	2	3-79	0	0	0	0	0	0	18
	-	3	2-80	0	0	0	0	0	0	1
	F	1	5-68	0	0	0	0	+	0	-
3	ab	2	5-75	0	0	0	0	+	0	75
	*M	3	1-80	0	0	0	0	0	0	66
	ab	1	-73	0	0	0	0	0	0	-
4	ab	2	-74	0	0	0	0	0	0	9
	*M	3	5-77	0	0	0	0	0	+	36
	*M	1	2-78	0	0	0	0	0	0	-
5	ab	2	12-79	0	0	0	0	0	0	11
	-	3	9-80	0	0	0	0	0	0	6
6	*M	1	6-77	0	0	0	0	+	+	-
	-	2		+	0	0	0	+	+	28
7	*F	1	12-76	0	0	0	0	0	0	-
	*M	2	3-80	+	0	+ 3-4 m.	0	0	0	30

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
8	M	1	11-78	0	0	0	0	0	0	-
	*F	2	2-80	0	0	0	0	0	0	6
	F	1	3-79	0	0	0	0	0	0	-
	M	2	9-72	0	0	0	0	+	0	21
9	F	3	2-74	0	0	0	0	+	0	8
	*F	4	3-77	0	0	0	+ 2 tri.	+	0	28
	-	5	3-80	0	0	0	0	0	0	27
10	*F	1	9-78	0	0	+ 5-6 m.	0	0	+	-
	F	1	4-78	0	0	0	0	0	0	-
11	ab	2	2-79	0	0	0	0	0	0	1
	*F	3	12-79	0	0	0	0	0	0	8
12	*M	1	1-79	+	0	0	0	0	0	-
13	*M	1	10-77	0	0	0	0	+	0	-
	F	1	10-75	0	0	0	0	0	0	-
14	*F	2	8-75	0	0	0	0	+	0	13
	F	3	10-79	0	0	0	0	0	0	17

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
15	*F	1	1-77	0	0	0	0	0	0	-
		2		0	0	0	+ cold - time unk.	0	0	-
16	*M	1		0	0	0	0	+	0	-
	ab	1		+	0	0	0	0	+	-
17		2	8-77	0	0	0	0	0	+	-
	*F	3	8-80	0	0	0	0	0	+	27
	M	1	2-53	0	0	0	0	0	0	-
	M	2	5-54	0	0	0	0	0	0	6
18	F	3	12-55	0	0	0	0	0	0	10
	M	4	12-59	0	0	0	0	0	0	39
	*F	5	6-63	0	0	0	0	0	0	33
	M	1	6-69	0	0	+	0	0	0	-
19	*F	2	7-74	0	0	+ 3 m.	0	0	0	52
	ab	3	8-78	0	0	0	0	0	0	60
20	F	1	2-75	+	0	0	0	0	0	-
	*F	2	6-80	0	+	0	0	0	0	55

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	M	1	-62	0	0	0	0	0	0	-
21	*F	2	-63	0	0	0	0	0	0	6
	F	3	-69	0	0	0	0	0	0	-
	M	4	-71	0	0	0	0	0	0	-
22	M	1	1-57	0	0	0	0	0	0	-
	*F	2	5-59	0	0	0	0	0	0	19
	F	1	5-52	0	0	0	0	0	0	-
23	*F	2	5-53	0	0	0	0	0	0	15
	F	3	6-55	0	0	+	0	0	0	22
	M	4	3-58	0	0	0	0	0	0	33
	F	1	8-75	0	0	0	0	0	0	-
24	ab	2	-78	0	0	0	0	0	0	32
	*F	3	2-79	0	0	0	0	0	0	1
	ab	4	9-80	0	0	0	0	0	0	10
	M	1	7-53	0	0	0	0	0	0	-
25	ab	2	-54	0	0	0	0	0	0	-
	F	3	7-58	0	0	0	0	0	0	51
	*F	4	11-59	0	0	0	0	0	0	6

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	M	1	5-70	0	0	0	0	0	0	-
26	ab	2	-73	0	0	0	0	0	0	36
	M	3	2-75	0	0	0	0	0	0	30
	*F	4	3-76	0	0	0	0	0	0	4
	F	1	9-70	+	0	0	0	0	0	-
27	F	2	7-73	+	0	0	0	0	0	25
	*M	3	7-79	+	0	0	0	0	0	63
	M	1	10-62	0	0	0	0	0	0	-
28	F	2	3-64	0	+	0	0	0	0	8
	*M	3	11-66	+	+	0	0	0	0	23
	F	1	8-60	0	0	0	0	0	0	-
29	*F	2	9-61	0	0	0	0	0	0	4
	*F	3	9-62	0	0	0	0	0	0	3
	F	4	8-64	0	0	0	0	0	0	14
30	M-M*	1	9-52	0	0	0	0	0	0	-
	F	2	6-55	0	0	0	0	0	0	24
31	*M	1	6-65	0	0	0	0	+	0	-
	M	2	10-70	0	0	0	0	+	0	56

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	*M	1	8-67	+	0	0	0	0	0	-
32	M	2	7-69	0	0	0	0	0	0	14
	F	3	3-72	0	0	0	0	0	0	23
33	*M	1	5-79	0	0	0	0	0	+	-
	F	1	2-60	0	0	0	0	0	+	-
	F	2	12-61	0	0	0	0	0	+	-
33	ab	3	-62	0	0	0	0	0	+	13
	*M	4	7-63	0	0	0	0	0	+	4
	F	5	12-64	0	0	0	0	0	+	8
35	F	1	11-76	+	0	0	0	0	0	-
	*F	2	11-78	0	0	0	0	0	0	13
36	*M	1	3-77	+	0	0	0	0	0	-
	-	2	2-80	+	0	0	0	0	0	26
37	M	1	9-56	0	0	0	0	0	+	-
	*F	2	8-61	0	0	0	0	0	+	50

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	ab	1	-52	0	0	0	0	0	0	-
	F	2	9-54	0	0	0	0	0	0	12
	F	3	1-56	0	0	0	0	0	0	12
38	F	4	1-57	0	0	0	0	0	0	9
	M	5	3-59	0	0	0	0	0	0	17
	*M	6	5-63	0	0	0	0	0	0	41
	ab	7	-64	0	0	0	0	0	0	12
	F	1		0	0	0	0	0	0	-
39	F	2		0	0	0	0	0	0	24
	*M	3		0	0	0	0	0	0	24
	ab	1		0	0	0	0	0	0	-
40	*F	2	11-64	0	0	0	0	0	0	60
	ab	3		0	0	0	0	0	0	-
	ab	4		0	0	0	0	0	0	-
	F	1	7-51	0	0	0	0	0	0	-
41	F	2	6-54	0	0	0	0	+	0	26
	*F	3	3-64	0	0	0	0	+	+	108
	F	1	10-40	0	0	0	0	+	0	-
42	*F	2	12-42	0	0	0	0	+	0	11
	M	3	10-46	0	0	0	0	+	0	15

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
	F	1	2-56	0	0	0	0	+	0	-
43	F	2	9-58	0	0	0	0	+	0	22
	*F	3	9-59	0	0	0	0	+	0	3
	M	4	6-61	0	0	0	0	+	0	12
	F	1	12-77	0	0	0	0	0	0	-
44	ab	2	9-79	+	0	0	0	0	0	20
	*M	3	9-80	0	0	0	+ 10 wks.	0	+	3
45	*F	1	8-78	0	0	0	0	0	0	-
46	*F	1	8-78	0	0	0	0	+	0	-
	M	2	5-80	0	0	0	0	+	0	12
	M	1	11-42	0	0	0	0	0	0	-
47	*M	2	5-47	0	0	0	0	0	0	45
	F	3	12-53	0	0	0	0	+	0	46
	F	1	12-51	0	0	0	0	0	0	-
	M	2	4-53	0	0	0	0	0	0	31
	*M	3	1-57	0	0	0	0	0	0	12
48	M	4	5-58	0	0	0	0	0	0	7
	M	5	10-60	0	0	0	0	0	+	20
	ab	6	7-65	0	0	0	0	0	0	48
	*M	7	9-66	0	0	0	0	0	0	5

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
49	*F	1		0	+	0	0	0	0	-
50	*F	1	1-71	0	0	+ 3 m.	0	0	0	-
	M	2	7-76	0	0	0	0	0	0	57
	M	1	1-71	0	0	0	0	+	0	-
51	*M	2	11-76	0	0	0	0	+	0	48
	M	3	5-78	0	0	0	0	+	0	12
52	*F	1	3-75	0	0	0	0	0	0	-
	F	1	6-57	0	0	0	0	0	0	-
53	F	2	6-59	0	0	0	0	0	0	13
	F	3	11-61	0	0	0	0	0	0	20
	*F	4	2-76	0	0	0	0	0	0	173
54	*M	1	4-62	0	0	0	0	+	0	-
	F	2	7-65	0	0	0	0	0	0	30
55	*M	1	5-79	0	0	0	0	0	0	-
56	*M	1	12-79	0	0	+ time unk.	0	0	+	-

PREGNANCY HISTORY

GROUP: Control (con't)

PT. #	SEX	PG. #	B.D.	OC	HORMONES	FLU TIME	ILLNESS TIME	ANTI-EM.	OTHER	IPG
57	*M	1	3-76	0	0	0	0	0	0	-
	M	2	6-78	0	0	0	0	0	0	18
	M	1	6-61	0	0	0	0	0	0	-
	M	2	9-62	0	0	0	0	0	0	6
58	*M	3	9-63	0	0	0	0	0	0	4
	F	4	8-65	0	0	0	0	0	0	14
	*F	5	3-69	0	0	0	0	0	0	34
	F	1	12-75	0	0	0	0	0	0	-
59	F	2	6-77	+	0	0	+ strep throat	0	+	9
	*M	3	11-80	0	0	0	0	0	0	12

APPENDIX C

BACKGROUND INFORMATION

KEY TO ABBREVIATIONS AND SYMBOLS USED IN APPENDICES OF BACKGROUND DATA

Abbreviations:

GYN Problems = gynecological problems

Symbols:

= number

o = degree relative

0 = negative history

+ = positive history

– = not available or unknown

BACKGROUND INFORMATION

GROUP: Thoracic - Michigan Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	-	-	Swedish - English	Danish - English
2	0	0-	-	Irish - Welsh - Dutch	Italian - Irish
3	0	-	-	Dutch	Dutch
4	0	A+	AB-	Anglo mix	Italian
5	0	A+	-	German - Canad.	Jewish
6	0	B+	O+	Polish	Irish
7	0	B+	B+	French - English	German
8	0	O+	A+	English	English
9	0	AB-	A+	German	Polish - German
10	0	A+	B+	Anglo mix	German
11	0	-	-	Italian	Italian
12	0	A+	-	Anglo-Saxon	Anglo mix

BACKGROUND INFORMATION

GROUP: Thoracic - U.S. Data

PT. #	GYN PROBLEMS	BLOOD TYPES MATERNAL	BLOOD TYPES PATERNAL	ETHNIC ORIGIN MATERNAL	ETHNIC ORIGIN PATERNAL
1	0	0+	-	-	-
2	0	-	-	Croatian	Croatian
3	0	AB+	-	-	-
4	0	A-	A+	Anglo-Saxon	Italian - Polish
5	0	-	-	Anglo-Saxon	Anglo-Saxon
6	0	A+	A+	Irish - Lithuanian	Irish
7	0	A+	A+	English - French	Anglo-Indian
8	0	0+	0-	Anglo-Saxon	Anglo-Saxon
9	0	-	-	"American"	"American"
10	0	A+	A+	"American"	"American"
11	0	0+	0	German	German
12	0	A+	0	French - Norweg.	German - Dutch - English
13	0	-	-	English - German	English
14	0	0+	0+	Anglo-Saxon	Welsh
15	0	A-	0-	Hungarian	Slovak
16	0	A+	0+	"American"	"American"
17	0	0+	0+	Anglo-Saxon	Anglo-Saxon
19	+ irregular periods	A-	0+	Anglo-Saxon	Mexican

BACKGROUND INFORMATION

GROUP: Lumbar - Michigan Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	-	A+	A+	Anglo mix	Swedish - English
2	+	B-	A-	Polish	Greek - Scottish-Dutch
3	0	B-	A+	Polish	Polish
4	0	A+	-	Czech.	German
5	0	O+	AB+	-	-
6	0	O+	O+	American	American
7	0	-	-	German	-
8	0	A-	A-	Dutch	Dutch
9	+	B+	A+	French - Irish	Scottish - Irish-German
10	0	B+	AB	Polish - German	German
11	-	O+	-	German	German - Irish
12	0	B	-	English	English
13	0	B+	O+	Polish	Irish
14	0	A+	A-	Finnish	Danish
15	0	O+	O-	Finnish	English - Dutch-Irish
16	0	-	-	Dutch	Anglo-Saxon
17	-	-	-	-	-
18	0	-	-	Polish	English - French
19	0	-	O-	Irish - German Swedish	-

BACKGROUND INFORMATION

GROUP: Lumbar - Michigan Data (con't)

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
20	0	B+	A+	German	German
21	0	A+	A+	French - German	Polish - German-French
22	0	O+	A+	Anglo mix	Polish - German
23	0	-	-	Maltese	Polish
24	0	O-	A-	Dutch	French
25	0	A	O	Anglo-Saxon	German - English
26	0	O+	B-	Scottish	Irish - German
27	0	A+	O+	French - German	French - Dutch
28	0	O+	-	Anglo mix	Irish - French
29	0	O+	A+	Belgian - Dutch	Dutch - Belgian
30	0	O	B	Slovak	French - Indian - Irish
31	0	AB+	O+	English	German
32	0	O+	A+	Anglo mix	English
33	0	-	-	Italian	Italian
34	0	B-	O+	German - Hungarian	Polish
35	0	-	-	American	American
36	0	A+	O	English - German	-
37	0	A+	A+	Polish - German	German - British
38	0	-	-	English	English

BACKGROUND INFORMATION

GROUP: Lumbar - Michigan Data (con't)

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
39	0	B-	A+	English - French-German	Polish
40	0	O+	O+	Indian - Irish-French	Anglo-Saxon
41	0	A+	B	Irish - German	Italian
42	0	B+	O+	Italian	German
43	0	O+	B+	Anglo-Saxon	English - Swedish - German
44	0	O	-	German	German
45	0	O+	B+	Irish	Scottish
46	0	O+	O+	Anglo mix	English - German
47	0	B+	B+	Irish	Polish - Austrian
48	0	O+	AB+	Anglo mix	German - Polish
49	-	A+	B+	French - German	German
50	+	B+	A+	Scottish - Swiss	English

BACKGROUND INFORMATION

GROUP: Lumbar - U.S. Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	-	-	Polish	Italian
2	0	-	-	N.W. European	N.W. European
3	0	A+	AB+	German	German
4	0	AB-	O+	-	-
5	0	A-	O+	-	-
6	0	A+	A-	British	Dutch - English
7	0	A+	O+	German - English	English
8	0	B+	-	German - Dutch	German - Dutch
9	0	-	+	Irish - German	German
10	0	O+	AB+	Irish	Greek
11	+	O+	A-	Dutch	Anglo mix
12	0	AB+	O	Ukranian	Irish - German
13	0	O+	O+	Anglo-Saxon	German
14	0	O+	O+	English - German	German - Austrian
15	0	O+	O+	Amer. Indian - Scottish	Irish
16	0	AB-	O+	German - Polish	Dutch
17	0	A+	-	-	-
18	0	-	-	German - Luxemburg	Spanish - Irish
19	0	O+	-	German	German
20	0	O-	-	German - English	English

BACKGROUND INFORMATION

GROUP: Lumbar - U.S. Data (con't)

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
21	0	B+	O+	German - English	English - German
22	+	O+	O+	English - Dutch	German - Irish
23	+	-	O+	American	American
24	0	O+	B+	-	-
25	0	-	-	-	-
26	0	O+	A+	German - Danish	French - Indian
27	0	O+	-	-	-
28	0	O+	A-	Anglo mix	Anglo mix
29	0	O+	-	Anglo-Saxon	English
30	0	-	-	-	-
31	0	O+	A+	-	-
32	0	A-	B-	-	-
33	0	O-	-	-	-
34	+	A+	O+	French - English	Polish - German
35	0	-	-	-	-
36	0	A+	A	Irish - Indian	English - German
37	0	AB+	O+	-	-
38	0	-	-	-	-
39	0	O+	O+	-	-
40	+	-	-	-	-
41	0	A+	A+	Anglo-Saxon	German
42	0	-	-	-	-
43	0	AB+	O	Anglo-Saxon	Anglo-Saxon

BACKGROUND INFORMATION

GROUP: Lumbar - U.S. Data (con't)

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
44	0	O-	A+	French - Czech.	Anglo mix
45	0	A-	O-	American	American
46	+	-	B+	English	German
47	0	O+	O+	Anglo mix	German
48	0	B+	B+	Irish - German	English - German
49	-	-	-	Anglo-Saxon	German - English
50	0	B+	B+	German - Anglo	German - French
51	0	A+	-	American	American
52	0	A-	A-	English - German	English - Italian
53	0	O+	O+	German - Swedish	German
54	0	-	-	Anglo-Saxon	Belgian - German

BACKGROUND INFORMATION

GROUP: Sacral - Michigan Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	-	-	English	English
2	0	-	-	French - Indian	-
3	0	-	A	French - English-Indian	Norwegian - French - Indian
4	+	A+	B+	Polish - German-Russian	Anglo - French
5	0	B-	B+	Polish - German	Anglo mix
6	0	-	-	German - Yugoslav	Irish - Swedish
7	0	A+	O+	German - English	German - English

BACKGROUND INFORMATION

GROUP: Sacral - U.S. Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	-	-	"American"	"American"
2	0	A+	B+	German - Dutch	German
3	0	B+	O+	Anglo-Saxon	Anglo-Saxon
4	0	O	O	German - Irish	German
5	0	O	O	German	German
6	0	O+	A+	N. European	English
7	0	A+	-		
8	+	AB+	A+	"American"	Mexican
9	0	A+	O+	"American"	"American"
10	+	O+	O+	Danish - German	Anglo mix
11	0	-	O+	Irish - Polish	Irish - French
12	0	A-	O+	Mexican	Polish
13	0	O+	B+	Spanish	Czech. - Italian
14	0	-	-	Norwegian	German - Anglo
15	0	B+	AB	Irish - Scottish	English

BACKGROUND INFORMATION

GROUP: Other - Michigan Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	A+	A-	German - Polish	German
2	0	B+	-	Finnish	German - Swedish
3	0	O+	B+	Finnish - Irish-Dutch	Finnish - Italian
4	+	A+	B+	Dutch	Dutch
5	+	O-	A+	Anglo mix	Dutch
6	0	A+	AB+	-	-
7	0	O+	O+	Anglo mix	Italian - German
8	0	A+	A+	Luthuanian - German - Irish	Italian - Polish
9	0	AB-	A-	American	American
10	+	-	-	Irish - Hungarian	German - Polish
11	+	A+	B+	French - Irish	Anglo-Saxon

BACKGROUND INFORMATION

GROUP: Other - U.S. Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	AB-	O+	Swedish - English	German - English
2	+	A+	O+	American	American
3	0	AB-	O+	Indian - Irish-Dutch	Anglo-Saxon
4	0	O+	-	Anglo mix	Anglo mix

BACKGROUND INFORMATION

GROUP: Encephalocele - Michigan Data

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	0	A+	O+	Anglo-Saxon	Anglo-Saxon
2	0	O+	A+	Slovak	French
3	+	O+	-	Anglo mix	Anglo mix
4	+	A+	-	Anglo mix	German
5	+	A+	A+	Anglo mix	Anglo mix
6	0	O+	AB+	Anglo-Saxon	Swedish - German
7	0	O+	O+	Anglo-Saxon	Anglo mix

BACKGROUND INFORMATION

GROUP: Control

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
1	+	B+	B+		
2	0	-	-		
3	0	O-	O-		
4	0	-	-		
5	0	-	+		
6	0	O+			
7	0	-	-		
8	0	A+	AB+		
9	0	O+	-		
10	0	O+	A+	Russian	German - Italian
11	0	A+	+		
12	0	O+	B+		
13	0	A+	A+		
14	0	O+	O+		
15	0	A+	A+		
16	+	A+	-	Dutch	German
17	0	A+	+	Irish	Italian
18	+	O+	-	German - Dutch	Dutch
19	0	A+	A+	German	Italian
20	0	B+	-	Russian	Polish
21	0	O+	O+	Anglo mix	English - German
22	+	-	-	-	Italian
23	0	-	-	French - Polish	Polish

BACKGROUND INFORMATION

GROUP: Control (con't)

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
24	0	A+	A+	German - Lithuanian	German
25	0	-	-	Hungarian	German
26	0	O+	O+	Dutch	American
27	0	A+	O-	German	Anglo mix
28	0	A	-	Italian	Polish
29	0	A+	-	Polish	Irish
30	+	-	-	Dutch - German	French - Scottish
31	0	A+	A+	German - Dutch	Dutch - English
32	0	O	O	American	American
33	0	B-	B+	French	German
34	+	-	-	-	-
35	0	O+	O-	American	Dutch
36	-	+	+	-	-
37	0	A	O	Anglo-Saxon	Anglo-Saxon
38	0	+	-	Anglo-Saxon	Anglo mix
39	-	B	B	-	-
40	0	A+	-	-	-
41	0	AB+	O+	Dutch	Dutch
42	0	-	-	English	Anglo-Saxon
43	0	-	-	-	Dutch

BACKGROUND INFORMATION

GROUP: Control (con't)

PT. #	GYN PROBLEMS	BLOOD TYPES		ETHNIC ORIGIN	
		MATERNAL	PATERNAL	MATERNAL	PATERNAL
44	0	O+	A+	German - Finnish	Austrian - German
45	0	-	-	American	American
46	0	0	B	French - Swedish	Polish - Dutch
47	+	A+	B-	Swedish - German	Dutch
48	0	AB+	O+	English - Indian	Dutch
49	+	-	AB+	Irish	German
50	0	A-	A+	German	German
51	0	A+	-	Dutch	German - Dutch
52	0	O+	AB-	Dutch	Dutch
53	0	O-	O-	German	English
54	0	A+	-	Dutch	Dutch
55	0	O+	-	-	-
57	0	-	-	-	-
58	+	+	+	Dutch	Dutch
59	0	A+	O+	Dutch	German - Irish

APPENDIX D

QUESTIONNAIRE

FAMILY HISTORY

Condition	Name and relationship	Birthdate	Age at onset	Where treated
Spina bifida, anencephaly, or encephalocele				
Hydrocephalus				
Back problems of any kind (include cysts or dimples)				
Scoliosis (curvature of the spine				
Congenital heart disease or defect				
Clubfoot or clubfeet				

FAMILY HISTORY (con't.)

Condition	Name and relationship	Birthdate	Age at onset	Where treated
Cleft lip/palate				
Digestive system defects (e.g., pyloric stenosis)				
Miscarriage or abortion (note how far along at the time of the loss				
Stillbirth (note cause, if known)				
Down's syndrome				
Any other significant family medical history				

QUESTIONNAIRE

PREGNANCY HISTORY AND BACKGROUND INFORMATION

1. What is the ethnic origin of the affected person's mother? _____ father? _____

2. What are the parents' blood types? Mother___Father___

3. Was the mother of the affected child exposed to any of the following environmental agents before or during the pregnancy that resulted in the birth of the child with spina bifida? At which point in the pregnancy or how long before conception?

agent	(check one) yes	no	when?
birth control pills			
fertility drugs (e.g., clomid)			
hormones (any kind)			
flu			
any viral illness			
anti-morning sickness medication			
any other medication			

If the mother was exposed to any of the above-mentioned agents during other pregnancies, please note that in the space below.

4. How long did it take for the parents to conceive?

5. Has the mother had any gynecological problems for which she has had to seek treatment?

6. Have either parent had back X-rays?_____ What were the results of those X-rays?

QUESTIONNAIRE

TOTAL NUMBER OF FAMILY MEMBERS

Total number of children (brothers and sisters of the child with spina bifida_____

List below:

Birthdate Sex

For each side of the family, please list the number of blood relatives in each category.

Relative	Mother's side	Father's side
Brothers		
Sisters		
Nieces		
Nephews		
Aunts		
Uncles		

Comments:

Mother's birthdate_____

Father's birthdate_____

QUESTIONNAIRE

This page is to provide information on your child's spina bifida. In order for this study to be informative, I need to know where the level of the spina bifida is)e.g., T-9 to T-12, T-10 through the sacrum, occipital encephalocele, etc.).

What is the level of your child's (or the affected person's) spina bifida?_____

What is the extent of involvement of the spina bifida? (E.g., does it include all of the lumbar spine and sacral spine if it is an L-2 level, or does it just include L-2 and L-3?)

If you do not know the level or extent of involvement, describe as best as you can where the spina bifida is located on the back, and what functions of the child are affected (e.g., does he/she have bowel or bladder control? Can he/she walk with braces? Can he/she walk at all?) Whatever information you can provide would be useful.

QUESTIONNAIRE

STATEMENT OF CONSENT

I heretofore agree to provide Helga Toriello and the Michigan State University Genetics Clinic with all pertinent medical records and my family history for the study entitled "Investigation of Heterogeneity Among Neural Tube Defects". I understand that there are no benefits to me, but that the results could be of use to medical science in the genetic counseling of other families. I also understand that all information gathered will be completely confidential, and that if published, all persons will remain anonymous. I am aware of the fact that I can withdraw from the study at any time, and all information gathered on my family will be accessible to me or my family physician, if we so desire.

Signature of participants _____

_____

_____

(parents of child and child if over the age of seven)

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