Journal of Medical Genetics, 1980, **17**, 203–211

A family study of spina bifida and anencephalus in Belfast, Northern Ireland (1964 to 1968)

N C NEVIN AND W P JOHNSTON

From the Department of Medical Genetics, The Queen's University of Belfast, Belfast, Northern Ireland

SUMMARY The parents of 226 of the 360 patients with anencephalus or spina bifida or both, born in Belfast 1964 to 1968, were visited to document the occurrence of these malformations among other relatives. The proportions of sibs with anencephalus and spina bifida were 10·42% for spina bifida index patients and 6·47% for anencephalus. For patients born after the index patients, the proportions were 12·19% and 6·35%, respectively. The overall incidence of either malformation among sibs was 8·87%. This estimate is higher than the 4 to 5% commonly reported and is probably related to the specific background of the Northern Ireland population, which is known to have the highest incidence of CNS malformations in the United Kingdom. The substantial size of this risk indicates the importance of amniocentesis for monitoring subsequent pregnancies of women who have had one child with a CNS malformation.

This family study is based on patients with spina bifida and anencephalus, born between the years 1964 and 1968, inclusive, in Belfast, Northern Ireland. Details of the area, method of ascertainment, and biosocial factors are given in Elwood and Nevin.[1 2] The total births were 41 351, of which 360 patients had a central nervous system (CNS) malformation: 151 had anencephalus; 185 had spina bifida; and 24 had anencephalus with spina bifida. The incidence of anencephalus, which includes the group having anencephalus with spina bifida, was 4·2, and of spina bifida 4·5 per 1000 total births, giving an overall incidence of these two malformations of 8·7 per 1000 total births. This incidence is the highest so far reported and exceeds that of South Wales, another high incidence area in the United Kingdom, where the incidence of the two malformations is 4·1 and 3·5, respectively.[3]

Methods

For a study of familial aggregation, only cases ascertained in Belfast for 1964 to 1968 were included. However, owing to the 'troubles' in Northern Ireland and the increased movement of population, it was only possible to trace 226 of the 360 (62·8%) of the original cohort. Of the 185 (76 male, 109 female) patients with spina bifida, 134 (61 male and 73 female) were contacted, and of the 175 (46 male and 129 female) with anencephalus or anencephalus with spina bifida, 92 (25 male and 67 female) were traced. The parents of the index patients were visited. Family histories were obtained and in many instances were confirmed or supplemented by visits to other relatives. The family history included information on sibs, parents, grandparents, aunts, and uncles. Affected or possibly affected relatives were documented from hospital records or death certificates or both. Summary family histories are given in appendix 1.

Received for publication 4 October 1979

Results

RECURRENCE RISKS FOR SIBS

The outcome of all the pregnancies of the mothers of the index patients are listed in table 1. They had a total of 874 pregnancies yielding 710 sibs, of whom 63 (8·87%) had anencephalus or spina bifida. The percentage of affected sibs was higher (10·42%) when the index case had spina bifida than when it had anencephalus (6·47%). The rate among previous sibs was 35 in 420 (8·33%) and the rate among subsequent sibs was 28 in 290 (9·66%). There were 176 spontaneous abortions, a rate of 25·2%.

Spina bifida

The findings in the sibs of the spina bifida index

TABLE 1 *Outcome of pregnancies of women having at least one child with a CNS malformation, Belfast 1964–1968*

	Index patient		*Total*
	Anencephalus	*Spina bifida*	
No of index patients	92	134	226
No of singleton sibs	264	419	683
No of twin pregnancies	7	8†	15
Total No of sibs	278	432	710
No of anencephalus or spina bifida sibs	18	45	63
Affected sibs (%)	6·47	10·42	8·87
No of spontaneous abortions	68*	108	176
% of pregnancies	25·09	25·29	25·21

*One was a twin pregnancy. †Index patient in three sets of twins.

patients are shown in table 2. Of 246 brothers, 15 (6·10%) had spina bifida, and seven (2·85%) had anencephalus. Of 186 sisters, 18 (9·68%) had spina bifida, and five (2·69%) had anencephalus. The total incidence of either malformation was 8·94% in brothers and 12·36% in sisters; the total incidence in sibs of either sex was 10·42%.

Analysis by sex of the index patient shows that for males, 28 of 209 (13·40%) sibs, and for females, 17 of 223 (7·62%) sibs were affected. Among sibs born before the index patient, the proportion of sibs affected was 25 of 268 (9·33%) and among the sibs born after the index patient the proportion of sibs affected was 20 of 164 (12·19%). There were 31 families in which the index patient was the result of the first pregnancy; among the subsequent 46 sibs, four (8·69%) had a CNS malformation. In families in which the index patient was not the first conception, of 386 subsequent sibs 41 (10·62%) had a CNS malformation. There is no significant difference in the percentage of sibs affected in these groups ($\chi^2 = 0{\cdot}02; 0{\cdot}9 > p > 0{\cdot}8$).

Anencephalus

The findings in the sibs of index patients with anencephalus are shown in table 3. There were 92 index patients, 25 males and 67 females. Of 149 brothers, seven (4·70%) had spina bifida and four (2·68%) had anencephalus. Of 129 sisters, two (1·55%) had spina bifida and five (3·88%) had anencephalus. The total incidence of either malformation was 7·38% in brothers and 4·70% in sisters, and the total incidence in sibs of either sex was 6·47%. One older sister of a female index patient had congenital hydrocephalus.

On analysis by sex of index patient, eight of 76 (10·53%) of sibs of male index patients and 10 of 202 (4·95%) of sibs of female index patients were affected. Among the sibs born before index patients, 10 of 152 (6·58%) were affected, and among those born after the index patient eight of 126 (6·35%). There were 23 families in which the index patient was the result of the first pregnancy: among the

TABLE 2 *Brothers and sisters of index patients with spina bifida distinguishing those born before and those born after index patients*

Index patient		*Brothers*						*Sisters*					
		Older		*Younger*		*Total*		*Older*		*Younger*		*Total*	
		Total	*Affected*	*Total*	*Affected*	*Total*	*Affected*	*Total*	*Affected*	*Total*	*Affected*	*Total*	*Affected*
Male	61	71	3 A 1 SB	47	2 A 5 SB	118	5 A 6 SB	54	3 A 6 SB	37	2 A 6 SB	91	5 A 12 SB
Female	73	87	1 A 6 SB	41	1 A 3 SB	128	2 A 9 SB	56	0 A 5 SB	39	0 A 1 SB	95	0 A 6 SB
Total	134	158	4 A 7 SB	88	3 A 8 SB	246	7 A 15 SB	110	3 A 11 SB	76	2 A 7 SB	186	5 A 18 SB

TABLE 3 *Brothers and sisters of index patients with anencephalus distinguishing those born before and after index patients*

Index patient		*Brothers*						*Sisters*					
		Older		*Younger*		*Total*		*Older*		*Younger*		*Total*	
		Total	*Affected*	*Total*	*Affected*	*Total*	*Affected*	*Total*	*Affected*	*Total*	*Affected*	*Total*	*Affected*
Male	25	21	0 A 1 SB	16	1 A 2 SB	37	1 A 3 SB	21	3 A 0 SB	18	0 A 1 SB	39	3 A 1 SB
Female	67	56	2 A 2 SB	56	1 A 2 SB	112	3 A 4 SB	54	1 A 1 SB 1 H	36	1 A 0 SB	90	2 A 1 SB 1 H
Total	92	77	2 A 3 SB	72	2 A 4 SB	149	4 A 7 SB	75	4 A 1 SB 1 H	54	1 A 1 SB	129	5 A 2 SB 1 H

subsequent 51 sibs, three had a CNS malformation (3·88%). In the families in which the index patient was not the first conception, of 227 sibs 15 (6·61%) had a CNS malformation. There is no significant difference in the percentage of sibs affected in these groups ($\chi^2 = 0{\cdot}02; 0{\cdot}9 > p > 0{\cdot}8$).

RECURRENCE RISKS FOR FIRST COUSINS

The findings in cousins are summarised in table 4. A comparison is made with the numbers of CNS malformations expected if the incidence had been that found in the general population for the area. Among 2293 cousins of index patients with spina bifida, 13 had a CNS malformation, whereas 20 would have been expected. It was only in the case of spina bifida among cousins that the number affected (11) approached the number expected (10). The rate for maternal cousins was higher (7·67 per 1000) than for paternal cousins (3·57 per 1000). Of 1698 cousins of index patients with anencephalus, 15 would have been expected to have a CNS malformation and 13 were found to be affected. The rate for maternal cousins and for paternal cousins were similar, 7·50 and 7·80 per 1000, respectively. The overall incidence of CNS malformations among cousins was 6·51 per 1000. For paternal cousins 11 in 2017 (5·45 per 1000), and for maternal cousins 15 in 1974 (7·60 per 1000) were affected.

TABLE 4 *Cousins of index patients showing number with spina bifida and anencephalus*

	Spina bifida			*Anencephalus*		
	SB	*A*	*Total*	*SB*	*A*	*Total*
Mother's brother's children	5	0	524	1	0	361
Mother's sister's children	2	2	650	4	1	439
Total	7	2	1174	5	1	800
Expected	5·3	4·9		3·6	3·4	
Father's brother's children	4	0	499	6	0	395
Father's sister's children	0	0	620	1	0	503
Total	4	0	1119	7	0	898
Expected	5·0	4·7		4·0	3·8	

TABLE 5 *Uncles and aunts of index patients showing number with spina bifida and anencephalus*

	Spina bifida			*Anencephalus*		
	SB	*A*	*Total*	*SB*	*A*	*Total*
Maternal						
Uncles	2	0	314	0	0	210
Aunts	2	0	299	1	0	211
Paternal						
Uncles	1	0	278	1	0	205
Aunts	2	0	300	2	0	206
Total	7	0	1191	4	0	832

RECURRENCE RISKS FOR SECOND DEGREE RELATIVES

Information on aunts and uncles was difficult to document as records were usually not available. The findings on uncles and aunts are shown in table 5. Among the 1191 uncles and aunts of index patients with spina bifida, seven had spina bifida (5·9 per 1000), and among the 832 uncles and aunts of index patients with anencephalus, four had spina bifida (4·8 per 1000). The lack of anencephalus cases among uncles and aunts was probably the result of parents of an anencephalic child usually being told that the child was stillborn.

CONSANGUINITY OF PARENTS

Only two index patients were born to consanguineous parents (206,356). In one the parents were first cousins, and in the other second cousins. Of the 13 sibs in the latter family, none had a CNS malformation. In the other family, the only other pregnancy ended as a spontaneous abortion.

NON-CNS MALFORMATIONS AMONG SIBS

The sibs with malformations other than those of the central nervous system are shown in appendix 2. Among 710 sibs, 15 had a major congenital malformation. These included three patients with congenital dislocation of the hip, two with pyloric stenosis, one with microcephaly, one with Down's syndrome, one with talipes equinovarus, one with cleft palate, one with congenital heart defect, one with imperforate anus, bilateral talipes equinovarus, imperforate urethra, and absent scrotum and penis, one with oesophageal atresia, one with oesophageal atresia and congenital heart defect, one with oesophageal atresia, tracheo-oesophageal fistula, common atrium, coarctation of the aorta, dilatation of the bladder, and bilateral hydronephrosis, and one with hare lip, cleft palate, and congenital heart disease.

Discussion

The present study was undertaken to assess the risk of spina bifida and anencephalus among sibs of index patients with these malformations. The proportion of affected sibs is in good agreement with that found in other United Kingdom studies. Table 6 compares the proportion of affected sibs in major surveys in the United Kingdom over the past 15 years. The proportion of affected sibs in the present survey is 8·87%. This estimate is higher than the 4 to 5% commonly reported, and may be because of the background of the Ulster population which is known to have the highest incidence of these

TABLE 6 *UK studies in population incidence and proportion of sibs affected*

	Index patient	*Population incidence (%)*	*Sibs with CNS malformation*	*%*	*Relative to population*
Southampton[6]	Spina bifida	0·32 } 0·51	7/119 5·89	5·63	× 11·0
	Anencephalus	0·19 }	2/41 4·89		
South Wales[3]	Spina bifida	0·41 } 0·76	52/854 6·09	5·18	× 6·8
	Anencephalus	0·35 }	29/709 4·10		
Greater London[7]	Spina bifida	0·15 } 0·29	25/730 3·42	4·45	× 15·3
	Anencephalus	0·14 }	41/754 5·44		
Glasgow[5]	Spina bifida	0·28 } 0·56	25/450 5·56	5·64	× 10·1
	Anencephalus	0·28 }	26/454 5·73		
Belfast	Spina bifida	0·45 } 0·87	45/432 10·42	8·87	× 10·2
	Anencephalus	0·42 }	18/278 6·47		

malformations in the world. In Belfast (1964 to 1968) the incidence was 8·7 per 1000 total births,[1] and more recently 7·6 per 1000 total births.[4] However, when the percentage of affected sibs relative to the population incidence is examined, the findings in Belfast are similar to those of Glasgow[5] and of Southampton.[6] The proportion of affected sibs, which is ten times the population incidence, is greater in London,[7] and less in South Wales.[3] The size of this risk among sibs of affected subjects indicates the importance of genetic counselling and prenatal diagnosis in monitoring pregnancies of women who have had an infant with a CNS malformation.

There was a higher proportion of affected sibs of spina bifida than of anencephalic index patients. A similar finding was noted in the South Wales[3] and in the Southampton[6] surveys, whereas the reverse was observed in the London[7] and Glasgow[5] studies. However, the differences were not significant. The recurrence risks among sibs before and after the index patient were similar, 8·3% and 9·7%, respectively. This is in agreement with other family studies (table 7).

The recurrence rate after two affected children is higher than after one.[8] Since a certain proportion of spontaneous abortions are the result of a CNS malformation in the fetus,[9 10] one would expect a higher recurrence rate if a preceding pregnancy had resulted in a spontaneous abortion. The recurrence rate was calculated according to whether the mother had had a spontaneous abortion before the index patient (table 8). In sibships with at least one spontaneous abortion before the index patient, the proportion of affected sibs was 1 in 11·2, whereas, if the index patient was the first pregnancy, or if

TABLE 7 *Recurrence risks among sibs before and after the index patients*

	Previous sibs	*Subsequent sibs*	
Williamson[6]	6/106 (5·7%)	3/55 (5·5%)	$\chi^2=0·0947;0·8>p>0·7$
Carter *et al*[3]	45/1023 (4·4%)	26/539 (4·8%)	$\chi^2=0·0652;0·8>p>0·7$
Carter and Evans[7]	38/877 (4·3%)	28/607 (4·6%)	$\chi^2=0·0166;0·9>p>0·8$
Janerich and Piper[11]	9/295 (3·1%)	10/742 (1·4%)	$\chi^2=2·523;0·2>p>0·1$
Present paper	35/420 (8·3%)	28/290 (9·7%)	$\chi^2=0·2252;0·7>p>0·5$

TABLE 8 *Recurrence risks among offspring of mothers with an infant with a CNS malformation depending on outcome of pregnancies before the index patient*

Study	*Lesion in index patient*	*Outcome of pregnancies before index patient*		
		None	*Normal livebirths*	*Presence of at least one spontaneous abortion*
Belfast	Spina bifida	4 in 46 (1 in 11·5)	6 in 63 (1 in 10·5)	5 in 26 (1 in 5·2)
	Anencephalus	3 in 51 (1 in 17·0)	5 in 41 (1 in 8·2)	0 in 31 (—)
	Total	7 in 97 (1 in 13·9)	11 in 104 (1 in 9·5)	5 in 57 (1 in 11·2)
South Wales[3]	Spina bifida	8 in 156 (1 in 19·5)	4 in 96 (1 in 24·0)	1 in 46 (1 in 46·0)
	Anencephalus	3 in 117 (1 in 39·0)	4 in 77 (1 in 19·3)	4 in 35 (1 in 8·8)
	Total	11 in 273 (1 in 24·8)	8 in 173 (1 in 21·6)	5 in 81 (1 in 16·2)

only live births preceded the index patient, the proportion of affected sibs was 1 in 13·9 and 1 in 9·5, respectively. The difference in these three proportions was not significant ($\chi^2 = 0{\cdot}74;0{\cdot}98 > p > 0{\cdot}95$) and suggests that a history of a previous miscarriage is not an important factor in determining recurrence risk. The South Wales study[3] was analysed in a similar manner. The proportion of affected sibs in the three groups was 1 in 16·2, 1 in 24·8, and 1 in 21·6. Again, the difference in these three rates was not significant ($p = 0{\cdot}63$).

There is a tendency for an affected sib to have the same type of CNS malformation as the index patient (table 9). Of 46 families with two sibs with CNS malformations, 28 had similar and 18 dissimilar lesions.

TABLE 9 *Tendency for affected sibs to have the same CNS malformation as index patient*

Index patient	*Sib*		*Same : Different*
	Spina bifida	*Anencephalus*	
Spina bifida	22	10	28 : 18
Anencephalus	8	6	

This work was aided by grants from the Belfast, Lurgan, and Mid-Ulster Branches of the Association for Spina Bifida and Hydrocephalus. We are grateful to Mr David Bradley, Department of Medical Statistics, The Queen's University of Belfast for the statistical analyses.

APPENDIX 1 *Index patients and sibs*

*M, male; F, female; m, miscarriage; sb, stillbirth; * index patient; [ ], twins; (A), anencephalus; (S), spina bifida; (H), hydrocephalus.*

Serial No	*Sibship*	*Date of birth*	
		Mother	*Father*
A. SPINA BIFIDA			
One child families			
059	*F(S)7/64	1928	1926
067	*F(S)8/64	1929	1927
206	*F(S)3/66sb;m–/67	1937	1920
207	*F(S)7/66	1941	1936
347	*M(S)1/68	1947	1944
Two child families			
009	*F(S)1/64;M3/65	1942	1938
049	m6/59;m12/59;F5/61sb;m12/61;m3/62;m12/62;m4/63;*F(S)6/64	1932	1929
105	*M(S)2/65;M1/68	1939	1940
117	*F(S)4/65;F3/67	1946	1937
128	F5/60;*M(S)8/65	1928	1926
148	m–/62;F8/63;*M(S)8/65sb	1931	1934
160	*F(S)10/65;M1/70	1945	1943
165	*M(S)10/65;M2/67	1947	1946
167	*F(S)11/65;m5/67;m9/67;m1/70;M4/71	1944	1944
200	M3/61;*M(S)2/66sb	1935	1927
231	*F(S)7/66sb;M5/70	1947	1945
235	*M(S)7/66;F11/71	1942	1941
262	M2/63;*M(S)12/66	1932	1930
264	*F(S)7/66;M9/70	1941	1940
269	M7/62;*F(S)2/67sb	1942	1938
288	M10/65;*M(S)4/67	1941	1936
307	M9/62;*F(S)7/67	1939	1938
319	*M(S)9/67;F8/72	1949	1947
351	*F(S)3/68;F10/70	1945	1947
366	*F(S)11/68;M7/72	1948	1939
374	F1/57;*M(S)2/68	1931	1929
382	F8/60;*F(S)5/68	1934	1930
521	*F(S)7/68;M6/74	1945	1947
Three child families			
007	F5/56;F5/60;*F(S)1/64	1925	1925
010	M1/57;m7/60;*F(S)1/64;M5/66;m9/68	1935	1934
023	F2/63;*F(S)3/64;F2/70	1940	1942
038	M9/49;m6/53;F4/58;*M(S)5/64	1927	1920
043	M7/50;m6/51;m8/52;M4/55;m8/60;m4/63;*M(S)6/64	1926	1925
050	M3/58;M4/60;*F(S)7/64	1928	1926
062	M8/61;m4/62;m2/63;*F(S)8/64;M5/67	1939	1934
119	F4/60;*M(S)5/65;m–/66;m–/67;M12/68;m12/72	1934	1938

APPENDIX 1—*continued*

Serial No	*Sibship*	*Date of birth*	
		Mother	*Father*
Three child families—continued			
125	F7/63;m5/64; *M(S)6/65;F12/68	1942	1943
199	*F(S)2/65;F1/67;F6/69;m1/71	1932	1933
209	*F(S)3/66sb;m11/66;F12/67;F9/69	1936	1937
216	*M(S)4/66;m–/67;M(S)2/68 No 520;F5/72;m3/73	1940	1942
217	F5/56;F5/57;*M(S)4/66	1926	1931
233	M(S)1/59;F5/61;*F(S)7/66	1936	1929
243	*M(S)9/65;F(A)8/66sb No 268;F2/70	1944	1946
244	*F(S)12/65;M10/66;m–/68;F5/70	1942	1942
252	M6/65;*M(S)9/66;M1/70	1944	1942
256	*F(S)10/66;F12/67;m–/68;F1/70	1946	1944
310	*F(S)7/67sb;M3/69;F(S)3/72	1942	1943
344	M4/57;F11/58;*F(S)1/68	1926	1921
345	F3/58;F3/60;*F(S)1/68	1937	1933
358	M6/66;*F(S)6/68;F9/70	1947	1944
360	F3/65;F7/66;*F(S)8/68	1946	1945
362	F11/65;M5/67;*M(S)9/68	1943	1934
370	M2/67;*F(S)1/68;M12/68	1946	1943
372	F5/62;M11/64;*F(S)1/68	1940	1936
519	F9/67sb;*M(S)10/68;M5/71	1945	1945
520	M(S)4/66 No 216;m–/67;*M(S)2/68;F5/72;m3/73	1940	1942
Four child families			
005	M11/54;F7/56;F(S)9/61;*F(S)1/64;m5/67	1934	1931
011	m5/46;m2/47;M6/48;M3/52;M2/57;*F(S)1/64	1924	1923
016	F(A)9/61sb;M8/62;*M(S)2/64sb;m7/65;M(A)4/67 No 286	1939	1934
021	F12/58;M4/60;M2/62;*M(S)3/64	1935	1936
024	m1/62;M(A)10/62sb;*M(S)10/64;F(S)10/66 No 245;m8/68;F2/70	1938	1943
064	*M(S)8/64;m12/64;M1/66;F5/69;F5/72	1943	1940
086	m2/56;m6/56;m9/57;M3/59;m4/60;m1/61;M2/62;m–/63;m–/63;m2/64;*F(S)11/64;M7/66	1936	1929
087	*M(S)11/64;m4/65;F6/66,M6/67;M3/70	1938	1938
098	M4/62;m6/63;*M(S)1/64;F8/66;F7/67	1942	1941
102	M9/61;F9/62;F10/63;*F(S)9/64	1940	1940
133	F7/61;M7/62;*M(S)7/65;M8/69	1934	1933
161	M10/53;F4/57;F7/58;*M(S)10/65sb	1935	1930
162	M9/60;F3/62;*F(S)5/65;m2/69;M12/69	1928	1931
198	*F(S)2/66;M6/67;F8/68;M8/70	1944	1942
210	M12/54;F5/62;M6/64;*M(S)1/66	1923	1911
242	M3/61;M5/62;M8/63;*F(S)8/66	1938	1937
245	m1/62;M(A)10/62sb;M(S)10/64 No 024;*F(S)10/66;m12/67;m8/68;F2/70	1938	1935
276	*F(S)7/67;F3/69;F3/71;F8/72	1942	1938
302	F2/64;F6/65;*M(S)7/67;M2/72	1945	1942
316	M7/63;m–/66;*M(S)8/67sb;M4/69;M2/72	1940	1938
339	M2/64;F12/65;*M(S)12/67;M11/70	1944	1944
383	F8/66;*M(S)6/68;M8/70;F11/71	1931	1922
386	*F(S)7/67;M12/68;M(A)4/71sb;M10/72	1934	1939
388	M6/64;*M(S)4/67;M12/68;F(A)4/70sb	1937	1938
407	F4/65;*F(S)6/68sb;F9/69;F11/71	1940	1935
Five child families			
013	m2/63;*M(S)2/64;M2/65;M6/66;M5/67;M(S)6/69;m1/70	1941	1935
014	M9/63;*M(S)4/64;F(S)12/65sb No 115;m–/67;m–/69;M5/70;M3/72	1944	1941
111	M12/46;M10/49;M6/58;*M(S)3/65sb;F2/67	1925	1925
112	M1/61;F2/62;M4/63;*M(S)3/65;F6/66	1928	1925
115	M9/63;M(S)4/64 No 014:*F(S)12/65sb;m–/67;m–/69;M5/70;M3/72	1944	1941
116	F11/48;M3/51;*M(S)5/65sb;M7/67;M11/69	1930	1932
135	M6/55;M4/57;F1/69;F8/60;*F(S)7/65	1935	1934
138	F1/61;M10/62;*F(S)10/65;F10/67;F6/71	1938	1935
140	F1/62;M(S)8/63;M7/64;*F(S)11/65;F4/69	1940	1940
188	M(S)11/63;m12/63;M1/65;*F(S)3/66;M2/67;F1/70	1942	1943
189	*F(S)1/66;F11/66;M10/67;F10/68;M12/71	1942	1943
191	M2/63;F(A)11/64 No 95;*M(S)1/66;F7/68;F1/70	1939	1937
208	M12/44;[F5/57;M5/57];M6/60:*M(S)3/66	1923	1928
214	m2/62;M(A)10/63sb;M11/64;*M(S)4/66;F7/68;F(S)11/72	1939	1938
236	F4/58;F3/59;M10/61;M12/63;m–/64;m–/65;*F(S)6/66	1934	1935
266	M11/54;M7/57;F4/49;F5/61;*F(S)1/67	1937	1935
315	M10/64;F8/66;*F(S)8/67;M8/68;m4/70;F5/71	1947	1944
384	F(S)1/61;M3/62;M2/65;*F(S)5/67;F2/69	1935	1933
Six child families			
004	M1/61;*F(S)1/64;M1/65;M7/66;M8/67;M8/69	1938	1941
045	m2/54;M2/55;F9/56;m3/57;F7/58;m3/61;M4/63;*M(S)6/64;M5/66	1935	1930

APPENDIX 1—*continued*

Serial No	*Sibship*	*Date of birth*	
		Mother	*Father*
Six child families—continued			
051	M7/61;F10/62;*F(S)7/64;F10/65;M12/67;F3/69	1937	1937
100	M7/59;M8/60;F2/62;M6/63;*F(S)1/65;F6/60	1934	1932
127	M4/56;M11/57;F(S)2/60;M4/63;*F(S)6/65;M(S)8/66 No 182	1939	1939
141	F12/55;M5/58;F7/61;M5/63;*M(S)12/65;F8/69sb	1932	1931
143	F3/62;M5/63;M4/64;[*F(S)8/65;M8/65];M6/68	1937	1934
181	M11/61;m–/62;F10/64;*M(S)12/65;M5/66;M5/68;F(S)3/71	1942	1942
182	M5/56;M11/57;F(S)2/60;M4/63;F(S)6/65 No 127;*M(S)8/66	1939	1939
186	F5/63;F6/64;*F(S)1/66;F4/67;M11/68;M6/71	1943	1941
248	M2/64;M(A)6/65sb No 124;*M(S)9/66;m–/67;[M(A)5/69sb;M5/69];M11/70	1941	1933
291	M4/59;M9/60;m–/61;M1/62;M9/65;*F(S)5/67;m–/69;M7/72	1927	1926
322	M12/61;M11/64;[*M(S)10/67;F(S)10/67];F8/70;M(S)2/71	1942	1940
324	M9/64;F(A)1/66 No 253;*M(S)7/67;M3/69;M6/71;M4/74	1934	1936
326	m4/57;M8/58;M11/61;m–/62;F4/63;M9/65;*F(S)10/67;M1/71	1939	1934
350	M1/57;m–/57;[F2/58;F2/58];F6/60;M1/62;*M(S)3/68	1939	1935
517	M8/64;F9/65;M9/66;*F(S)1/68;F2/69;m–/70;m–/70;m–/70;M(S)1/74	1947	1943
Seven (+) child families			
015	F10/59;F4/61;M8/62;*M(S)2/64sb;[M4/65;M4/65];M6/67	1930	1926
018	M2/54;F12/54;F8/56;M9/59;M10/61;M2/63;*M(S)2/64	1932	1929
031	M1/58;M10/59;M10/60;F10/62;*F(S)4/64;F11/66;m8/67;F2/71	1935	1931
044	M8/51sb;M6/52sb;M4/55;M10/57;M4/60;F2/63;*F(S)6/64;F6/67	1926	1921
052	F10/54;F12/55;M2/56sb;M1/58;F(S)4/59;M8/60;m4/61;F(S)2/62;*M(S)7/64;F10/69	1935	1933
076	m5/56;M3/57;m12/57;F(S)1/59;M6/60;m12/60;M7/62;m5/63;*M(S)9/64;m–/65;F7/66;F11/69	1935	1929
096	m10/63;*M(S)12/64;M1/66;m6/66;F8/67;F7/68;M(S)4/70;M(S)8/71;F(S)1/74	1940	1932
106	M3/58;M12/59;F12/60;F6/62;F2/63sb;*F(S)2/65sb;F12/68	1939	1937
136	F7/47;M2/49;M7/51;m–/52;F–/54;m–/55;M4/56;M–/61;m–/64;*F(S)8/65	1926	1926
178	M8/64;*F(S)12/65;M3/66;M(S)9/68sb No 516;F5/69;M12/70sb;m10/71;F2/74;m8/75	1944	1943
226	M11/48;F1/51;M5/52;F(S)9/53;m11/54;M12/55;M10/57;M(S)2/60;m8/60;F2/62;m3/63;m6/64; m9/64;m3/65;*F(S)6/66;m–/67;m–/68;F6/70	1926	1922
254	M5/65;[M9/66;*M(S)9/66];F4/68;M5/69:M7/70;M9/71	1944	1941
280	F11/57;M10/58;M10/60;M10/61sb;M2/64;*M(S)3/67;M12/70sb	1936	1933
356	F9/48;F–/53;m–/54;M4/55;m–/55;M9/56;F10/58;M1/60;F10/61;F12/63;[F12/64;F12/64]; F3/67;*M(S)5/68;F1/69;M6/70	1930	1935
368	F4/55;F9/56;M4/58;F4/60;M10/61;F6/64;m1/66;*F(S)11/68	1932	1928
403	m1/56;F1/57;M12/59;F4/61;F2/63;F10/64;F3/66;*F(S)3/68sb	1934	1933
504	M1/54;M3/56;m–/57;m–/58;M5/59;m–/60;M7/61;F(S)11/62sb;M5/66;m–/67;*F(S)8/68	1932	1934
516	M8/64;F(S)12/65 No 178;M3/66;*M(S)9/68sb;F5/69;M12/70sb;m10/71;F2/74;m8/75	1944	1943

B. ANENCEPHALUS

One child families			
227	m–/60;*M(A)6/66sb	1921	1921
397	m–/65;*F(A)2/68sb	1945	1944
Two child families			
037	F9/44;m6/49;*F(A)5/64sb;m–/64	1923	1919
040	*F(A)8/64sb;m10/66;M6/70	1935	1936
123	M4/63;*M(A)5/65sb	1935	1930
139	M8/63;m5/64;*F(A)8/65sb;m–/67	1925	1928
168	*F(A)2/65sb;F(A)11/66sb No 221	1940	1932
180	*F(A)12/65sb;m9/66;F3/68	1941	1941
219	*F(A)5/66sb;F4/68	1945	1942
220	F9/64;*F(A)5/66sb	1947	1947
221	F(A)2/65sb No 168;*F(A)11/66sb	1940	1932
285	m–/64;F(H)2/65;*F(A)7/66sb	1942	1940
289	F9/62;*F(A)3/67sb	1926	1927
306	*M(A)7/67;F(S)6/70sb	1939	1945
338	F8/62;m8/64;*F(A)11/67	1937	1937
378	m2/56;m–/57;F12/63;m–/64;*F(A)3/68	1935	1929
385	*F(A)6/68;F9/69	1944	1942
511	m1/68;*F(A)10/68sb;M12/71	1942	1939
522	M(A)7/59sb;m4/60;*F(A)12/68sb	1939	1935
Three child families			
137	M8/60;M6/62;*F(A)2/65sb	1932	1928
154	*F(A)9/65sb;F5/67;M1/70	1944	1943
157	F(A)10/58sb;M3/62;*M(A)8/65sb;m–70	1939	1932
159	M6/62;m–/63;M12/64;*M(A)7/66sb	1934	1934

APPENDIX 1—*continued*

Serial No	*Sibship*	*Date of birth*	
		Mother	*Father*
Three child families—continued			
183	F(S)6/61;*F(A)1/66sb;M2/70	1936	1935
193	m–/65;*M(A)1/66sb;[M7/67;M7/67]	1943	1943
195	F10/64;*F(A)1/66sb;F8/70	1937	1935
197	*F(A)2/66;M8/67;M8/71	1947	1946
211	M6/62;m–/63;M12/64;*M(A)7/66sb	1934	1934
256	*F(A)10/66sb;F12/67;m–/68;F1/70	1946	1944
257	*M(A)11/66;F11/67;M6/69	1946	1946
267	m–/59;F1/61sb;m1/63;M1/64;m–/66;*F(A)6/67sb	1933	1931
268	M(S)9/65 No 243;*F(A)8/66sb;F2/70	1946	1944
271	*F(A)1/67sb;M1/68;M4/71	1947	1946
272	F1/65;*M(A)1/67sb;F3/69	1932	1931
334	F12/66;*F(A)11/67sb;m3/68;F3/69;m1/71;m7/71	1943	1942
335	*M(A)11/67sb;F3/69;M5/70	1945	1945
336	*F(A)10/67sb;M4/69;M7/71	1947	1946
375	F2/62;*F(A)2/68;M7/70	1939	1939
399	M4/62;*M(A)3/68sb;M12/71	1936	1935
401	*M(A)3/68sb;F4/69;M5/72	1945	1942
500	*F(A)7/68sb;M1/70;M8/71	1941	1942
501	m–/67;*M(A)8/68sb;F8/69;F3/71	1948	1946
510	*F(A)10/68sb;m–/68;M3/71;M2/72	1950	1949
514	M12/66;*F(A)12/68sb;m12/69;F3/71	1940	1936
Four child families			
071	M7/56;M9/57;F7/60;*F(A)9/64sb	1933	1931
074	*F(A)9/64sb;F5/67;M9/68;M6/70	1944	1939
078	m6/63;*M(A)9/64;M12/65;[F10/66;F10/66]	1939	1939
079	F7/63;*M(A)9/64sb;M9/65;M(S)5/69	1932	1935
130	M(A)3/60sb;M(S)7/61;M7/63;*F(A)7/65	1937	1938
131	M3/47;M9/50;M12/59sb;*F(A)8/65sb	1924	1921
155	F9/63sb;m4/64;*F(A)9/65sb;M5/68;M11/70	1942	1938
156	*F(A)10/65sb;F9/66;m–/67;M(A)7/68sb No 408;M1/72	1945	1946
203	F10/61;*F(A)3/66;F12/69;M2/72	1935	1935
249	F12/61;M4/64;*F(A)9/66;M12/67	1941	1943
261	F12/64;*M(A)12/66;M8/68;F9/69	1934	1940
273	*F(A)2/67;F5/68;M1/70;F5/71	1946	1945
286	F(A)9/61sb;M8/62;M(S)2/64sb No 016;m7/65;*M(A)4/67	1939	1934
292	F1/60;M5/62;M6/64;*F(A)6/67sb	1926	1920
300	F8/65;*F(A)6/67sb;F4/69;M8/71	1945	1944
309	F7/66;*F(A)7/67sb;F9/68;M10/71	1931	1923
328	F8/52;F8/53;m–/54;M8/59;m–/60;m–/61;m9/65;*F(A)9/67sb	1930	1928
329	M8/64;M10/65;*F(A)9/67;m8/68;m8/69;F11/70	1940	1941
406	F4/58;M3/61;M5/64;*M(A)6/68sb	1938	1937
408	F(A)10/65sb No 156;F9/66;m–/67;*M(A)7/68sb;M1/77	1945	1946
Five child families			
006	*M(A)1/64sb;m6/64;m11/64;M10/65;F4/67;F5/69;F1/72	1942	1942
030	*F(A)4/64sb;F5/65;F3/67;M6/69;M11/70	1942	1937
039	m1/56;M11/57;M6/59;*F(A)5/64;M4/66;m2/68;F1/70	1931	1923
058	F3/61;m6/63;*F(A)7/64sb;F12/65;M3/67;F4/68	1939	1935
075	M8/61;M1/62;*F(A)9/64sb;M1/67;M12/68	1930	1929
094	[F7/57;M7/57];[F8/58;M8/58];*F(A)12/64sb	1932	1933
095	M2/63;*F(A)11/64sb;M(S)1/66 No 191;F7/68;F1/70	1939	1937
118	*F(A)4/65;F9/66;M10/68;M1/71;F2/72	1946	1946
132	*F(A)7/65sb;F9/66;F1/67;[M1/69;M1/69]	1931	1933
205	M1/64;*F(A)3/66;M3/67;F7/69;F7/70	1944	1938
270	m–/60;M5/61;M5/62;M3/64;*M(A)1/67sb;F4/69	1932	1932
301	M8/54;M3/57;m–/60;M4/61;*F(A)7/67sb;M6/68	1930	1929
Six child families			
124	M2/64;*M(A)6/65sb;M(S)9/66 No 248;m–/67;[M(A)5/69sb;M5/69];F11/70	1941	1933
147	M2/63;m6/63;F6/64;*F(A)9/65sb;m3/66;M5/67;M5/69;M2/70	1938	1938
163	m–/61;F2/63;m–/63;M7/64;*F(A)11/65sb;M12/66;F12/67;M3/70	1942	1934
251	M12/60;F12/61;F6/64;F5/65;*F(A)8/66sb;m–/68;M7/69	1940	1942
253	M9/64;*F(A)1/66;M(S)7/67 No 324;M3/69;M6/71;M4/74	1934	1936
506	M9/60;M8/61;F12/62;F1/64;m–/64;F11/65;*F(A)9/68	1938	1937
Seven (+) child families			
032	M1/58;M10/59;M10/60;F10/62;*F(A)4/64sb;F11/66;m8/67;F2/71	1935	1933
048	F7/54;M7/56;F12/57;M4/61;F11/62;*M(A)6/64sb;M11/65;m2/67;F2/68	1933	1934
056	M3/48;F1/49;F7/50;M11/51;F7/53;M12/60;*F(A)7/64sb	1925	1922

APPENDIX 1—*continued*

Serial No	*Sibship*	*Date of birth*	
		Mother	*Father*
Seven (+) child families—continued			
099	F4/59;F6/60;F11/61;M7/63;*F(A)1/65sb;M5/66;M10/70	1936	1933
142	M1/53;M10/54;F2/56;F2/57;F12/57;m–/59;M1/60;m–/61;F9/62:*M(A)4/65sb;F4/65;F10/66	1930	1931
175	F1/50;M12/50;M4/52;F9/53;F8/54;M10/55;M9/56;F11/57;m–/58;M4/60;F9/61;M12/62; *F(A)12/65sb;M4/68	1926	1921
222	F2/60;F5/61;m–/62;M6/65;*F(A)3/66sb;m9/67;[M2/69;M2/69];M2/70	1936	1932
230	F12/56;F3/59;M6/60;M12/62;m–/63;m–/63;F7/64;*F(A)7/66sb;M10/67;F12/68	1939	1935
398	F10/49;M4/51;F10/53;F7/54;F7/56;F9/59;F9/63;m4/64;m–/67;m–/67;*M(A)2/68sb	1933	1933
507	[m–/55;m–/55];F3/56;F4/57,F9/58;F2/60;M11/62;F6/63;M8/65;*F(A)9/68sb	1927	1928

APPENDIX 2 *Malformations (other than CNS malformation) in sibs of index patients*

Serial No	*Sibship*	*Malformation*
Spina bifida index patient		
076	F11/69	Congenital dislocation of hip
087	M3/70	Bilateral congenital dislocation of hip
133	F7/61	Microcephaly
209	F9/69	Mental retardation
252	M6/65	Imperforate anus, bilateral talipes equinovarus, imperforate urethra, absent scrotum and penis
350	M1/57	Mental retardation
358	M6/66	Pyloric stenosis
368	F9/56	Cleft palate
382	F8/60	Congenital heart defect
386	F10/72	Down's syndrome
407	F9/69	Congenital dislocation of hip
Anencephalus index patient		
075	M1/62	Talipes equinovarus
079	M9/65	Oesophageal atresia, tracheo-oesophageal fistula, common atrium, coarctation of aorta, dilatation of bladder, bilateral hydronephrosis
142	F4/65	Hare lip, cleft palate, and congenital heart defect
230	F7/64	Pyloric stenosis
328	F8/52	Mental retardation
406	M3/61	Oesophageal atresia
513	F7/72	Oesophageal atresia and absent right ventricle

References

1 Elwood JH, Nevin NC. Factors associated with anencephalus and spina bifida in Belfast. *Br J Prev Soc Med* 1973;**27**:73–80.

2 Elwood JH, Nevin NC. Anencephalus and spina bifida in Belfast (1964–1968). *Ulster Med J* 1973;**42**:213–22.

3 Carter CO, David PA, Laurence KM. A family study of major central nervous system malformations in South Wales. *J Med Genet* 1968;**5**:81–106.

4 Nevin NC, McDonald JR, Walby AL. A comparison of neural tube defects identified by two independent routine recording systems for congenital malformations in Northern Ireland. *Int J Epidemiol* 1978;**7**:319–21.

5 Richards IDG, McIntosh HT, Sweenie S. A genetic study of anencephaly and spina bifida in Glasgow. *Dev Med Child Neurol* 1972;**14**:626–39.

6 Williamson, EH. Incidence and family aggregation of major congenital malformations of the central nervous system. *J Med Genet* 1965;**2**:161–72.

7 Carter CO, Evans K. Spina bifida and anencephalus in Greater London. *J Med Genet* 1973;**10**:209–34.

8 Carter CO, Roberts JAF. The risk of recurrence after two children with central nervous system malformations. *Lancet* 1967;**1**:306–8.

9 Creasy MR, Alberman ED. Congenital malformations of the central nervous system in spontaneous abortions. *J Med Genet* 1976;**13**:9–16.

10 MacHenry JCRM, Nevin NC, Merrett JD. Comparison of central nervous system malformations in spontaneous abortions in Northern Ireland and South-East England. *Br Med J* 1979;**1**:1395–7.

11 Janerich DT, Piper J. Shifting genetic patterns in anencephaly and spina bifida. *J Med Genet* 1978;**15**:101–5.

Requests for reprints to Professor N C Nevin, Department of Medical Genetics, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland.