CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM*

II—MATERNAL REPRODUCTIVE HISTORY AND FAMILIAL INCIDENCE

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In a previous communication (Record and McKeown, 1949) we described an investigation of 930 consecutive malformations of the central nervous system certified as the causes of stillbirths or of first year deaths in the City of Birmingham in the years 1940-1947. Certain data were available for all these malformations in the Maternity and Child Welfare Department's records; additional information was obtained by home visits from 742 mothers of 755† of the 930 malformations, and from a control group of 742 mothers of 757 of the 892 infants born free from malformation, selected by taking every two hundredth name from the registers of live births and stillbirths for the same years. For a fuller discussion of the material and for an account of the procedure followed in classification of the malformations, we refer the reader to the earlier paper.

The most interesting observations so far recorded in this inquiry concerned the association of age and parity of the mother with the risk of birth of a central nervous malformation. We now make use of the information obtained by field inquiry to compare the malformation series and the control series in respect of the reproductive history of the mother, and the familial incidence of malformations of the central nervous system.

1. REPRODUCTIVE HISTORY OF THE MOTHER

The possibility that the uterine environment contributes to the appearance of congenital malformations was first discussed at a time when there was little precise information about the physiology of reproduction in mammals. Mall and his contemporaries were impressed by the high incidence of malformations observed in ectopic pregnancies, but they had few facts to guide them in seeking corroborative evidence of the contribution of the uterus. The work of endocrinologists during the past 30 years has placed at our disposal an acceptable account of the physiology of the pituitary, ovary, uterus, and mammary gland in the oestrous or menstrual cycle, and in pregnancy and lactation. So far there has been neither experimental nor clinical confirmation of the relevance of this knowledge to the problem of

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† 755 malformed propositi derived from families with 1 malformed propositus, 730; families with 2 malformed propositi, 11; families with 3 malformed propositi, 1. Total, 742.

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malformations; but the fact that the different phases of reproductive activity are closely inter-related suggests that if the uterus in which the malformed foetus develops is abnormal, there may be other evidence of abnormality in the history of reproduction. We have therefore examined the histories of mothers in the malformation and control series in respect of (a) menstruation, (b) age at marriage, (c) results of other pregnancies, (d) lactation, (e) fertility.

The relevant data to which we have access were recorded by interrogation of mothers visited at home, and it is evident that not too much weight can be placed on their accuracy. We have, in fact, restricted the examination to questions in which it was considered that errors of reporting were unlikely to be so great as to obscure gross differences between the two groups.

(a) *Menstruation*.—Table I (overleaf) shows that there are no appreciable differences in age at onset, length of cycle, or duration of flow, between mothers in the malformation and control groups. When the three main types of malformation are considered separately, there are also no noteworthy differences in the menstrual history of the mothers.

(b) *Age at Marriage*.—Since late conceptions may be associated with late marriages, the examination of age at marriage was suggested by Penrose's report that the risk of birth of a central nervous malformation is associated with high maternal age (Penrose, 1946), a result confirmed in this inquiry for hydrocephalus, but not for anencephalus or spina bifida. There is indeed some evidence that women who give birth to these malformations are on the average a little older than other women when they marry: the mean age at marriage was 23.01 for mothers of malformations, and 22.45 for mothers of controls (difference: 0.56 ± 0.20 years).

It is, of course, evident that the distributions of malformations and controls may differ in respect of the time of marriage, in which case before accepting an age difference it is necessary to satisfy ourselves that there has been no conspicuous increase in the age at marriage in recent years.* Data given by the Registrar-General for England and Wales for the years 1931 to 1946 indicate that on the contrary there has been a slight reduction of the mean age at marriage (Table II, overleaf). It should be noted that our observations for Birmingham are based on fertile marriages only, which may explain a mean age at marriage considerably below the national figure for spinsters. Widows, who are less fertile and older, are excluded.

(c) *Results of other Pregnancies*.—It is known that mothers who have given birth to a congenital malformation face a greater than average risk of malformed births in later pregnancies, and this is certainly true of the central nervous group (see Section 2). It has also been reported (Malpas, 1937) that rates of abortion, still-birth, and neonatal death are higher in families which have included malformations

* As mothers of malformations are later shown to be not less fertile than mothers of non-malformed births (see under (e)), the fact that primiparity is more common among mothers of malformations (see Part I) suggests that their marriages may be more recent.

TABLE I
MENSTRUAL HISTORY OF MOTHERS OF 755 MALFORMATIONS AND OF 742 CONTROLS

Menstruation	Type of Malformation						Controls	
	Anencephalus No.	Spina Bifida No.	Hydro- cephalus No.	Others No.	Total			
					No.	%	No.	%
<i>Age at Onset (years)</i>								
10 and under	4	5	2	0	11	1.5	13	1.8
11	14	17	5	0	36	4.8	44	6.0
12	38	47	9	4	98	13.0	92	12.6
13	68	72	20	8	168	22.4	150	20.5
14	75	83	38	6	202	26.9	203	27.7
15	58	45	23	3	129	17.2	124	16.9
16	31	25	13	1	70	9.3	74	10.1
17	11	8	5	1	25	3.3	23	3.1
18 and over	5	5	2	0	12	1.6	9	1.2
TOTAL	304	307	117	23	751	100	732	100
Age unknown	1	2	1	—	4		10	
Mean	13.9	13.7	14.1	13.7	13.8		13.8	
<i>Length of Cycle (days)</i>								
10-14	1	1	0	0	2	0.3	3	0.4
15-19	6	1	0	0	7	0.9	7	0.9
20-24	28	19	7	1	55	7.3	49	6.6
25-29	233	259	98	20	610	80.8	589	79.5
30-34	25	16	5	2	48	6.4	60	8.1
35-39	5	6	4	0	15	2.0	12	1.6
40+	7	7	4	0	18	2.4	21	2.8
TOTAL	305	309	118	23	755	100	741	100
Length unknown	—	—	—	—	—		1	
Mean	27.8	27.9	28.3	27.7	27.9		28.0	
<i>Duration of Flow (days)</i>								
1-2	10	7	5	1	23	3.1	21	2.8
3-4	90	94	43	11	238	31.7	256	34.5
5-6	135	152	44	7	338	45.0	301	40.6
7-8	60	53	23	4	140	18.6	156	21.1
9-10	7	2	0	0	9	1.2	5	0.7
11-12	0	0	1	0	1	0.1	1	0.1
13-14	0	0	0	0	0	0.0	0	0.0
15+	1	0	1	0	2	0.3	1	0.1
TOTAL	303	308	117	23	751	100	741	100
Duration unknown	2	1	1	—	4		1	
Mean	5.8	5.7	5.6	5.2	5.7		5.7	

of the central nervous system. The fact that these malformations usually lead to the death of the foetus *in utero* or shortly after birth clearly explains at least part of the increased foetal loss. Unfortunately since the causes of abortions are in

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TABLE II
MEAN AGE OF SPINSTERS AT MARRIAGE
(England and Wales, 1931–1946)

Year	Age at Marriage
1931–35	25.53
1936	25.61
1937	25.62
1938	25.58
1939	25.27
1940	24.97
1941	24.80
1942	24.59
1943	24.81
1944	24.84
1945	24.89
1946	25.44

general unknown, we are unable to consider whether the foetal loss is greater than could be explained by the high incidence of lethal malformations, and we can only report the dimensions of foetal loss when all known central nervous malformations are excluded. Table III gives this information for anencephalus, spina bifida, and hydrocephalus, and for all the malformations compared with the control series. The abortion rate is much higher for sibs of all these malformations than for sibs of controls; the stillbirth rate is higher for sibs of two malformations

TABLE III
RESULTS OF OTHER PREGNANCIES. (ALL KNOWN MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM ARE EXCLUDED)

	Malformations				All Malformations (a)	Controls (b)	Difference (a)–(b)
	Anen-cephalus	Spina Bifida	Hydro-cephalus	Others			
Live births surviving first year	514	591	222	31	1,358	1,244	
Live births dying in first year	31	37	12	2	82	77	
Total live births	545	628	234	33	1,440	1,321	
Stillbirths	30	14	23	1	68	31	
Total births	575	642	257	34	1,508	1,352	
Abortions	76	77	28	5	186	109	
Total conceptions	651	719	285	39	1,694	1,461	
Total foetal and infant loss	137	128	63	8	336	217	
Infant mortality rate per 1,000 live births	56.9	58.9	51.3		56.9	58.3	-1.4 ± 8.9
Stillbirth rate per 1,000 total births	52.2	21.8	89.5		45.1	22.9	$+22.2 \pm 6.8$
Abortion rate per 1,000 known conceptions	116.7	107.1	98.2		109.8	74.6	$+35.2 \pm 10.3$
Total infant and foetal death rate per 1,000 known conceptions	210.4	178.0	221.1		198.3	148.5	$+49.8 \pm 13.6$

Stillbirth and infant mortality rates for Birmingham (1940–47) were 26.8 and 51.3 respectively. The rates for the controls exhibited in Tables III and IV cannot strictly be compared with the rates for all births.

(anencephalus and hydrocephalus, but not spina bifida); infant mortality rates are not affected.

The material from Table III was reclassified by birth rank, since the magnitude of the rates is known to be associated with parity. When the rate of foetal and infant loss was standardized by applying the rates in each birth rank for malformations to the numbers in each birth rank for controls, the standardized rate was only slightly higher than the crude rate (198.9 compared with 198.3).

It has been reported (Murphy, 1940) that pregnancies immediately before and after the birth of a malformation are most likely to be disturbed. The sibs were therefore allotted birth rank positions in relation to the propositus: first, second, third, and fourth or earlier positions before the propositus; and first, and second or later positions after the propositus. The same rates of foetal and infant loss were calculated (see Table IV and Figure, opposite). The results suggest that the

TABLE IV
DATA FROM TABLE III REARRANGED IN RELATION TO POSITION OF PROPOSITUS

	Sibs of Malformations						Sibs of Control Propositi					
	Conceptions prior to Propositus				Conceptions subsequent to Propositus		Conceptions prior to Propositus				Conceptions subsequent to Propositus	
	4th+	3rd	2nd	1st	1st	2nd+	4th+	3rd	2nd	1st	1st	2nd+
Live births surviving first year	256	130	190	305	319	158	164	133	238	425	216	68
Live births dying in first year	18	6	8	29	18	3	20	11	15	22	7	2
Total live births	274	136	198	334	337	161	184	144	253	447	223	70
Stillbirths	18	5	12	16	15	2	2	3	5	11	6	4
Total births	292	141	210	350	352	163	186	147	258	458	229	74
Abortions	17	13	34	58	36	28	11	11	11	31	31	14
Total conceptions	309	154	244	408	388	191	197	158	269	489	260	88
Total foetal and infant loss	53	24	54	103	69	33	33	25	31	64	44	20
Infant mortality rate per 1,000 live births	65.7	44.1	40.4	86.8	53.4	18.6	108.7	76.4	59.3	49.2	31.4	28.6
Stillbirth rate per 1,000 total births	61.6	35.5	57.1	45.7	42.6	12.3	10.8	20.4	19.4	24.0	26.2	54.1
Abortion rate per 1,000 known conceptions	55.0	84.4	139.3	142.2	92.8	146.6	55.8	69.6	40.9	63.4	119.2	159.1
Total infant and foetal death rate per 1,000 known conceptions	171.5	155.8	221.3	252.5	177.8	172.8	167.5	158.2	115.2	130.9	169.2	227.3
Difference of total rate from mean	-26.9	-42.6	+22.9	+54.1	-20.6	-25.6	+19.0	+9.7	-33.3	-17.6	+20.7	+78.8
S.E. of difference	23.54	30.78	28.28	23.59	21.69	29.02	28.19	31.51	21.57	17.87	25.04	45.63

FIGURE.—Total foetal and infant loss at various birth ranks before and after the birth of the propositus.

conception immediately prior to the malformation experiences a greater loss than the others, due to higher rates of infant mortality and abortion, whereas among the control sibs this conception and the one preceding it have the lowest total death rates. The components that make up this loss have diverse trends.

(d) *Lactation*.—Enough is known about the physiology of pregnancy and lactation to make it profitable to inquire whether there is any association between the history of breast-feeding and the birth of malformations. It is conceivable that voluntary failure to breast-feed the young might have some later effect on the function of the uterus, or that mothers who give birth to congenital malformations are also less successful in feeding their children.

Our data permit a comparison of the proportions of infants breast-fed for different intervals in the malformation and control groups. The histories are recorded for live births preceding the malformed or control propositus, deaths in the first year of life being excluded. In this context infants are considered breast-fed if they are regularly at the breast, whether or not they also receive some complement of artificial food. Table V gives the information for the malformations and for

TABLE V
DURATION OF BREAST-FEEDING OF SIBS OF MALFORMATIONS AND CONTROLS BORN PRIOR TO THE PROPOSITI*

Sibs of Malformations										Sibs of Control Propositi	
Duration of Breast-feeding	Anencephalus		Spina Bifida		Hydrocephalus		Other	All			
	No.	%	No.	%	No.	%	No.	No.†	%	No.†	%
< 2 weeks ..	64	21.4	88	23.2	39	25.3	2	193	22.71	217	22.68
2 weeks— ..	62	20.7	62	16.4	16	10.4	4	144	16.94	194	20.27
3 months— ..	43	14.4	49	12.9	16	10.4	2	110	12.94	145	15.15
6 months and over	130	43.5	180	47.5	83	53.9	10	403	47.41	401	41.90
Total	299	100.0	379	100.0	154	100.0	18	850	100.00	957	100.00

* Deaths in the first year of life are excluded.

† $\chi^2 = 7.37$ $n = 3$ $0.05 < P < 0.10$

the controls, and exhibits no significant difference between the two distributions. Once again it seemed desirable to examine the data for birth ranks arranged in the order in which they preceded the birth of the propositus. In birth ranks closest to those of the propoiti a slight reduction was evident in the proportions of infants breast-fed six months in both the malformation and control series.

The histories of mothers in the control group cannot, of course, be taken as representative of the general population of mothers in respect of the manner of feeding their infants. Records relating to single births, or to deaths in the first year of life are excluded. This may account for the fact that the proportion of children fed at the breast for at least six months is higher than has generally been recorded in this country.

(e) *Fertility*.—The fallow periods between consecutive pregnancies of mothers in the malformation and control series were calculated as described below. For this purpose pregnancies resulting in abortions, stillbirths, and live births were included, with exceptions in the case of mothers unmarried at the time of conception.

- First births: (i) The relevant data at our disposal are the age at marriage, the date of the first birth, and the approximate duration of the first gestation in months.
- (ii) The date of the first conception was calculated.
- (iii) The fallow period was calculated as the number of months between the date of marriage and the estimated date of the first conception.
- Later births: (i) The relevant data at our disposal are the dates of birth of two consecutive pregnancies, and the approximate duration of each gestation in months.
- (ii) The date of conception of the second of the pregnancies was calculated.
- (iii) The fallow period was calculated as the number of months between the first birth and the estimated date of conception of the second.

The fallow period preceding first conceptions of second marriages was calculated from the date of that marriage.

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TABLE VI
MEAN PERIODS OF INFERTILITY (MONTHS) PRECEDING GESTATIONS

Type of malformation	Propositi			Sibs			Mean Size of family (1) + (2) (1)
	Number of gestations (1)	Sum of fallow periods	Mean fallow period	Number of gestations (2)	Sum of fallow periods	Mean fallow period	
Anencephalus	293	8,916	30.43	632	11,703	18.52	3.16
Spina bifida ..	287	7,448	25.95	688	11,343	16.49	3.40
Hydrocephalus	114	4,252	37.30	268	4,748	17.72	3.35
Other malformations ..	22	771	35.05	39	554	14.21	2.77
All malformations ..	716	21,387	29.87	1,627	28,348	17.42	3.27
Controls ..	710	23,844	33.58	1,338	26,517	19.82	2.88

Table VI gives the mean fallow period in months for the main groups of malformations, and for all malformations compared with controls. The mean is a little shorter for the malformations (29.87 months) than for the controls (33.58 months); the means for the individual malformations vary from 25.95 months for spina bifida to 37.30 months for hydrocephalus.

Table VI also records the same data for sibs of malformations and controls. The most striking feature of the table is that mean fallow periods are uniformly very much lower for sibs than for propositi, an observation which exposes an interesting source of error if the mean fallow period preceding births of malformations is compared with the mean fallow period preceding not-malformed births in the same families.* In this comparison each fraternity usually contributes to one side a single malformation; to the other side it contributes as many sibs as are recorded in the fraternity. It follows that the larger and more fertile the family, the greater is its representation among sibs, whereas its representation among the malformations usually remains unchanged at one. This source of error led Murphy (1940) to the conclusion that the birth of the malformed child was preceded by a period of relative sterility, a suggestion made earlier by Still (1927). Size of family also clearly affects the mean fallow period preceding births of sibs of the individual malformations; for example, if the mean size of family is smaller for anencephalus than for spina bifida, relatively fewer sibs are recorded from the smaller and less fertile families of anencephalics. It has therefore been necessary to examine the mean size of family, which is readily obtained by dividing the total number of births (propositi and sibs) by the total number of propositi. There are in fact slight differences in family size between the different malformations, and between the malformations and the controls.

We must now consider whether the mean fallow period is affected by birth rank. Table VII (overleaf) gives the data by birth rank for malformed and control propositi,

* This situation arises when no control group of births free of malformations is available for comparison.

TABLE VII
MEAN PERIODS OF INFERTILITY (MONTHS) PRECEDING GESTATIONS. DATA ARRANGED IN ORDER OF BIRTHS

Type of Malformation		Order of Birth												Total	
		1		2		3		4		5 and 6		7 and over			
		No. Gestations	Mean Fallow Period	No. Gestations	Mean Fallow Period	No. Gestations	Mean Fallow Period	No. Gestations	Mean Fallow Period	No. Gestations	Mean Fallow Period	No. Gestations	Mean Fallow Period	No. Gestations	Mean Fallow Period
Anen-cephalus	Pre-propositi	136	15·15	88	23·53	57	19·42	40	23·83	42	18·19	28	15·46	391	18·90
	Propositi	134	26·43	69	37·96	29	34·62	21	38·52	24	22·75	16	24·81	293	30·43
	Post-propositi	—	—	92	17·79	69	19·61	37	17·27	29	16·21	14	15·43	241	17·90
	Total	270	20·74	249	25·41	155	22·35	98	24·50	95	18·74	58	18·03	925	22·29
Spina bifida	Pre-propositi	138	11·22	103	19·81	61	20·41	39	19·62	45	16·38	42	16·90	428	16·46
	Propositi	121	19·32	60	34·90	43	25·93	23	36·52	19	30·37	21	23·05	287	25·95
	Post-propositi	—	—	86	17·06	70	17·04	40	15·90	37	18·30	27	12·04	260	16·53
	Total	259	15·00	249	22·49	174	20·42	102	21·97	101	19·71	90	16·88	975	19·27
Hydro-cephalus	Pre-propositi	59	10·32	48	19·33	28	25·61	21	22·00	21	24·33	15	17·60	192	18·18
	Propositi	40	26·80	29	49·31	16	34·25	8	57·75	12	42·50	9	25·56	114	37·30
	Post-propositi	—	—	26	15·46	25	17·20	12	18·67	8	16·88	5	13·20	76	16·54
	Total	99	16·98	103	26·80	69	24·57	41	28·00	41	28·20	29	19·31	382	23·56
Other malformations	Pre-propositi	12		2		2		1		2		1		20	13·15
	Propositi	7		12		1		1		—		1		22	35·05
	Post-propositi	—		7		10		2		—		—		19	15·32
	Total	19		21		13		4		2		2		61	21·72
Total malformations	Pre-propositi	345	12·65	241	21·19	148	20·86	101	21·68	110	18·36	86	16·49	1,031	17·64
	Propositi	302	23·62	170	39·16	89	29·97	53	40·57	55	29·69	47	24·36	716	29·87
	Post-propositi	—	—	211	17·16	174	18·04	91	16·63	74	17·32	46	13·20	596	17·05
	Total	647	17·77	622	24·73	411	21·64	245	23·89	239	20·65	179	17·71	2,343	21·23
Controls	Pre-propositi	416	13·79	251	22·33	147	22·42	77	26·82	65	22·31	30	16·30	986	18·91
	Propositi	230	25·66	216	38·88	109	37·49	72	37·33	61	37·48	22	22·00	710	33·58
	Post-propositi	—	—	110	27·47	98	20·03	59	21·86	54	19·65	31	17·39	352	22·37
	Total	646	18·02	577	29·51	354	26·40	208	29·05	180	26·65	83	18·22	2,048	24·59

as well as for gestations preceding and following these births. The data again direct attention to the error of a comparison between propositi and all their sibs.

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TABLE VIII
STANDARDIZED MEAN PERIODS OF INFERTILITY* (MONTHS) PRECEDING GESTATIONS

Type of Malformation	Propositi		Sibs		(a) ÷ (b)
	Number of gestations	Standardized mean fallow period (a)	Number of gestations	Standardized mean fallow period (b)	
Anencephalus	293	32.05	632	18.53	1.73
Spina bifida	287	27.88	688	16.12	1.73
Hydrocephalus	114	39.24	268	16.83	2.33
Other malformations ..	22	—	39	—	—
All malformations.. ..	716	31.59	1,627	17.18	1.84
Controls	710	33.58	1,338	19.82	1.69

* Mean periods of infertility for each malformation were standardized by applying the crude means to the numbers of controls in corresponding birth ranks.

Before proceeding to consideration of the effect of parity, we may also note that the fallow period is shorter for pregnancies following than for pregnancies preceding the malformations, which suggests that women who have given birth to a malformation are not deterred from further reproduction. In both the malformation and control series the mean fallow period is considerably shorter for first births, and for births after the sixth, and it is clearly desirable to standardize the results for birth rank before comparing mean fallow periods for all births. Table VIII shows standardized mean fallow periods for each malformation, obtained by applying the crude means to the numbers of controls in corresponding birth ranks. The mean fallow periods for the malformed propoiti are slightly increased by this treatment.

A rough index of the fertility of women before the birth of a propoitus relative to their fertility before other births, is given by the ratio of the mean fallow periods shown in Table VIII. This ratio is slightly higher for all malformations (1.84) than for controls (1.69), but is distinctly higher in the case of hydrocephalus (2.33). It was thought worth repeating this calculation after excluding first births, and when this was done the ratio for all the malformations was unchanged (1.84) and was higher than for the controls (1.66). The ratio for hydrocephalus was again distinctly raised (2.29). A further refinement was added by exclusion of pregnancies immediately following abortions, since it is reasonable to suppose that the period of infertility which follows will in general be shorter than after notified births, and since abortion is more common in families which include a malformation. The effects already noted were only slightly accentuated by this treatment. On this evidence there is little to suggest that women who give birth to malformations are less fertile than other mothers, or that malformations arise when births succeed each other too rapidly. There is some evidence, especially in the case of hydrocephalus, that women are slightly less fertile in the period preceding the birth of a malformation than in the period which precedes their other conceptions.

In view of the disrupting effect of the war on family life during the greater part of the period in which the births in this series occurred, a discussion on birth spacing would not be complete without reference to the periods of absence of the husband. The available data distinguished between service overseas in which home leave was rare, and service in Great Britain with occasional opportunity for cohabitation of husband and wife, but for simplification of the analysis both categories were considered together, absences for brief periods being disregarded. The data permitted a classification of all legitimate births into three groups: (a) families in which the father was absent during the year of birth of the propositus or during the preceding year; (b) families in which the father was not absent during the above period but was absent at some other time; (c) families in which the father was never absent. As might be expected, the results showed considerable variation with parity; when standardized for this variable they revealed no material differences between the malformation and control groups.

Although it is only remotely connected with the period of infertility, we may consider here the question of age differences between father and mother. On the average fathers were older than mothers by 2.4 years in the case of malformations, and by 2.9 years in the case of controls (difference: 0.5 ± 0.2). We have no reason to stress the importance of a difference of this magnitude, and it will be recalled that mothers of malformations were slightly older at marriage than other mothers. Murphy (1940) also examined this question and observed no significant difference.

2. FAMILIAL INCIDENCE OF MALFORMATIONS

(a) *Malformations in Fraternities.*—Appendix A (see p. 45) gives details of fraternities in the malformation group in which at least one other malformation among sibs was reported by the mother. We were unable to check the diagnoses of abortions (which are excluded from the analysis), but all diagnoses of stillborn and live born malformations in Birmingham were confirmed in central records for the years after 1936. The fraternities were arranged in three groups. Groups I and II include those in which other malformations involved the central nervous system and resulted in stillbirth or infant death, and Group III includes those in which other malformations were not of the central nervous system or did not lead to stillbirth or infant death.

Group I (12 fraternities). All the malformations (25) occurred in Birmingham in the years 1940-47, and all are in consequence included in the series of 755 malformed propositi.

Group II (16 fraternities). Only one malformation in each fraternity is included in the series of 755 malformed propositi. The other malformations were born outside the city, or outside the period 1940-47.

Group III (6 fraternities).

Appendix B (see p. 49) gives details of fraternities in the control group in which malformations among sibs were reported by the mother. It should be remembered that the controls were selected in such a way that lethal malformations of the

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TABLE IX
MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM AMONG ALL SIBS OF MALFORMED AND
CONTROL PROSITI

Group	Fraternities	Total Number* of Offspring	Proposit	Sibs of 742 Propositi	Number of Central Nervous Malformations among Sibs	Percentage of Sibs with Malformations of Central Nervous System
Malformations	742	2,276	742†	1,534	29	(a) 1·89
Controls	742	2,117	742	1,375	4	(b) 0·29

Difference between percentages, (a) - (b) = 1.60 ± 0.39

* Includes all notified live births and stillbirths, but excludes abortions.

† Includes only one malformed propositus from each fraternity.	The 755 malformed propositi born	
in the years 1940-47 were derived from:	Families with 1 malformed propositus	730
	" " 2 " " propositi	11
	" " 3 " " " "	1
		742

Thirteen malformed propiiti are here entered as sibs.

nervous system were excluded (Part I, Section 3). Only two of the control propositi had other and minor deformities. In one case (I, see p. 49) the second pregnancy resulted in an anencephalic stillbirth, and the fraternity is therefore included in both malformation and control series. In Part I it was estimated that 0·59 per cent. of all infants born in Birmingham in the years 1940-47 had malformations of the nervous system which resulted in stillbirths or infant deaths. Table IX shows that 1·89 per cent. of sibs of the malformed propositi are similarly affected, compared with 0·29 per cent. of sibs of the non-malformed control births. That is to say, the risk of birth of another central nervous malformation among sibs in the first case is about three times the average risk for all families, and in the second case is about

TABLE X
MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM AMONG ALL SIBS OF MALFORMATIONS OF
DIFFERENT TYPES

	Type of First Malformation				Total
	Anen- cephalus	Spina Bifida	Hydro- cephalus	Other	
Number of fraternities† 	302	300	116	23	741*
Sibs of 741 propoiti 	582	654	260	36	1,532
Number of central nervous malformations among sibs 	6	18	3	1	28
Percentage of sibs with malformations of the central nervous system 	1.03	2.75	1.15	—	1.83

* One fraternity (Appendix A, Group I, Fraternity "I") in which two twins had hydrocephalus is excluded from this and from subsequent tables. This explains the slight difference between Tables IX and X in the total percentages affected.

† This also gives the number of proposti here considered, since only one is entered from each fraternity.

TABLE XI
THE RELATIVE RISK OF RECURRENCE OF ANOTHER MALFORMATION OF THE SAME OR OF A DIFFERENT TYPE

Sibs of 741 propositi		Type of First Malformation												Total		
		Anencephalus			Spina Bifida			Hydrocephalus			Other					
		582			654			260			36			1,532		
Type of Subsequent Malforma- tion	Gen- eral Fre- quency in B'ham (1940- 47) per 100 Births	Act- ual No. (a)	Expec- ted No. (b)	(a) ÷ (b)	Act- ual No. (a)	Expec- ted No. (b)	(a) ÷ (b)	Act- ual No. (a)	Expec- ted No. (b)	(a) ÷ (b)	Act- ual No. (a)	Expec- ted No. (b)	(a) ÷ (b)	Act- ual No. (a)	Expec- ted No. (b)	(a) ÷ (b)
Anen- cephalus	0.23	3	1.35	2.2	7	1.51	4.6	1	0.60	1.7	0	0.08	11	3.54	3.1	
Spina bifida	0.25	2	1.43	1.4	10	1.61	6.2	1	0.64	1.6	0	0.09	13	3.76	3.5	
Hydro- cephalus	0.09	1	0.55	1.8	1	0.62	1.6	1	0.25	4.1	0	0.03	3	1.45	2.1	
Other mal- forma- tions	0.02	0	0.09		0	0.10		0	0.04		1	0.01	1	0.24		
Total	0.59	6	3.42	1.8	18	3.84	4.7	3	1.53	2.0	1	0.21	28	9.00	3.1	

When the three main types are considered together the risk of recurrence of the same malformation is given by the ratio $\frac{14}{3.21} = 4.4$; and the risk of a different malformation by the ratio $\frac{13}{5.35} = 2.4$.

half. Table X shows that the risk is relatively greatest for spina bifida (2.75 per cent.) and least for anencephalus (1.03 per cent.).

Where one malformation of the central nervous system has been recorded, it is of interest to know the relative risk of recurrence of another malformation of the same or of a different type. This information is contained in Table XI, in which the frequency of each malformation in Birmingham (see Part I, Table XIV) in the years 1940-47 has been used to calculate an expected number for comparison with the actual number observed. Two conclusions may be drawn for each of the three main central nervous malformations: (i) the risk of recurrence of the same malformation is greater than the risk of a different one; (ii) the risk of a different malformation is greater than the risk experienced by the general population of mothers.

When the three main types are considered together, the ratio of the actual to the expected rate of recurrence is 4.4 for the same malformation, and 2.4 for a different malformation.

We have so far considered only the risk of birth of a malformation for *all* sibs born *before* or *after* a propositus. In practice, however, the doctor is required to comment on the likelihood of recurrence *after* a malformation has been born, and this risk is assessed in Table XII (opposite). The data suggest that the risk of recurrence in subsequent sibs is about 1 in 20, almost nine times the risk in the general population of mothers. The risk is greatest where the earlier malformation is spina bifida. Moreover, it will be recalled that two of the three main groups

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TABLE XII

MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM AMONG SIBS BORN AFTER
A MALFORMATION HAS BEEN RECORDED

	Type of First Malformation				Total
	Anen- cephalus	Spina Bifida	Hydro- cephalus	Other	
Sibs born after the first malformation . .	214	247	65	15	541
Number of malformations	6	18	3	1	28
Malformation rate (per cent.)	2.80	7.29	4.62	—	5.18
Number of times by which these rates exceed the rate for Birmingham, 1940-47 (0.59%)	4.8	12.4	7.9		8.8

of central nervous malformations are commonest among first births and are therefore less common in births after the first than in all births. It follows that the comparison with the general population of mothers (as above) understates the relative risk for births after a malformation.

Finally we have used the information recorded in Appendix A (Group III) to obtain the incidence of other major malformations.* There were three of these (pyloric stenosis, imperforate anus, and congenital defect of the heart) among 1,505 sibs of malformations, giving a percentage incidence of 0.2. Among 2,112 sibs of controls there were nine major malformations (Appendix B) when those of the central nervous group (four plus one unspecified) were excluded, giving a percentage incidence of 0.43. The difference between the results for the two series is 0.23 per cent. ± 0.19 .

The literature contains a number of references to fraternities in which two or more malformations occurred. For malformations in general, including those for which genetic theory gives a satisfactory explanation, Macklin (1936) found a high rate of recurrence in a sibship. Murphy (1940) calculated that malformations affected one sib in every eight born subsequent to a malformation. In almost half of the fraternities in which a malformation recurred, the second malformation was identical with the first. It is noteworthy that in the forty fraternities which experienced a recurrence, 52 of the 91 malformations were defects of the central nervous system. Penrose (1939) records that among 1,041 sibs of malformations, there were 24 with congenital defect (2.31 per cent.). Included in this series was a group of 137 central nervous malformations, having 454 sibs of which ten were malformed (2.20 per cent.). The incidence of central nervous malformations among these 454 sibs was 1.54 per cent.

* Other major malformations here referred to are those (not involving the nervous system) which produce obvious disability at an early age, but do not necessarily lead to death. Other major malformations coexisting with central nervous defects in the same individual are excluded.

TABLE XIII
NUMBERS OF RELATIVES WHO WERE MALFORMED (SIBS EXCLUDED)

Type of Malformation of Propositus*	No. of Fraternities	Type of Malformation of Relative										Total Number of Malformed Relatives	
		Central Nervous System					Others Specified						
		Anen-cephalus	Spina Bifida	Hydro-cephalus	Others	Total	Special Senses	Hare-lip and/or Cleft Palate	Extre-mities	Others	Total		Un-specified
Anencephalus	302	6	8	1	1	16	4	4	5	—	13	5	34
Spina bifida ..	300	4	9	4	—	17	2	8	4	3	17	4	38
Hydrocephalus	117	—	3	—	—	3	—	2	—	—	2	1	6
Other mal-formations ..	23	—	1	—	—	1	—	1	—	—	1	—	2
Total	742	10	21	5	1	37	6	15	9	3	33	10	80
Controls ..	742	1	6	2	1	10	3	0	9	3	15	3	28

* Where more than one malformed propositus was recorded in a fraternity, the type of the first born was used for this classification.

Cases of recurrence of anencephaly in a sibship are not infrequent in the literature. Dunn and Salter (1944) quote ten references to this phenomenon and record a case which they observed where two successive foetuses in a sibship had anencephalus with spina bifida. A further case was reported by Quigley (1943). Among authors reporting recurrence of spina bifida are Pybus (1921) and Hindse-Nielsen (1938). In the latter's series, the propoiti had 548 sibs of whom 28 (5.1 per cent.) showed spina bifida aperta. Recurrence of hydrocephalus appears to be less commonly recorded. No mention of it was made in the 58 cases reported by Malpas (1937) or in the 43 cases published by Penrose (1939). Butler-Smythe (1889) reported one fraternity in which three children had hydrocephalus with spina bifida and the remaining two had abnormally large heads. Recurrence of hydrocephalus was noted in seven fraternities in the series published by Murphy (1940). Recurrence of central nervous malformations has also been reported in the litters of experimental animals (Snell and Picken, 1935; J. Hammond quoted by Boyd, 1942).

(b) *Malformations among other Relatives.*—Malformations among other relatives* were recorded at interview with mothers, but for various reasons the information must be accepted with reservations. First, mothers who have given birth to a malformed infant have a special interest in recalling other examples in their families; second, the person interviewed probably knows more about her own than about her husband's relatives; and third, it was not possible to confirm the type of malformation from central records (as in the case of lethal malformations in the same fraternities). Table XIII shows that eighty malformations of all types were recorded among relatives in 742 families in the malformation group, compared with 28 in 742 families of controls; of these defects, 37 and ten respectively involved the nervous system. The incidence among relatives is higher for anencephalus and spina bifida than for hydrocephalus (Table XIV, opposite).

* Other relatives here exclude sibs; they include parents, grandparents and great-grandparents of the propositus, and all other individuals sharing this common ancestry.

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TABLE XIV
PROPORTION OF FRATERNITIES, INCLUDING AT LEAST ONE MALFORMATION, WHICH HAVE MALFORMED RELATIVES

Type of Malformation of Propositus*	No. of Fraternities	Type of Malformation of Relative						Total	
		Involving C.N.S.		Not Involving C.N.S.		Unspecified			
		No.†	%	No.†	%	No.†	%	No.†	%
Anencephalus ..	302	16	5.3	10	3.3	4	1.3	30	9.9
Spina bifida ..	300	14	4.7	13	4.3	3	1.0	30	10.0
Hydrocephalus ..	117	2	1.7	2	1.7	1	0.9	5	4.3
Other malformations	23	1	4.3	1	4.3	0	—	2	8.7
All malformations	742	33	4.4	26	3.5	8	1.1	67	9.0
Controls	742	10	1.4	13	1.8	3	0.4	26	3.5

* Where more than one malformed propositus was recorded in a fraternity, the type of the first born was used for this classification.

† Differences in numbers in Tables XIII and XIV are explained by the few cases in which more than one relative of the same fraternity was malformed.

No doubt the difficulty of recording accurately the number and type of malformations among relatives at risk explains the scarcity of data on incidence. Single instances of recurrence in a family were reported for hydrocephalus (Butler-Smythe, 1889) and spina bifida (Dunn and Salter, 1944; Mills, 1949); but the most interesting data were the result of a large scale inquiry into spina bifida by Hindse-Nielsen (1938). This author noted 0.32 per cent. of affected relatives on the mother's side (fourteen out of 4,367), and 0.15 per cent. of affected relatives on the father's side (eight out of 5,365). Murphy (1940) in an investigation of relatives of malformations of all types also observed that the same defect recurred almost three times as often among the maternal relatives, although the incidence of individuals with a malformation of any type was about equal on the two sides. The difficulty of squaring such an observation with genetic theory led Morison (1945) to question the completeness of the records, and certainly before it is accepted as reliable a much more thorough examination of the problem is needed.

(c) *Consanguinity between Parents of Malformations.*—Three first-cousin marriages (i-iii) and one of second cousins (iv) were noted among parents of the 742 fraternities in the malformation group. Their offspring were as follows.

- (i) Four children, all born alive. Three children not affected; one child (the second), with hydrocephalus and congenital cataract, died at 14 days. Father had two children, both normal, by a previous marriage.
- (ii) Four children, all born alive. Three children not affected; one child (the fourth), with spina bifida, died at three weeks.
- (iii) A single child, stillborn, with spina bifida and hydrocephalus.
- (iv) Three children. Two live born, not affected; one stillborn (the second), with hydrocephalus.

For this series the consanguinity rate is 0.54 per cent., and 0.40 per cent. were first-cousin marriages. In the control series of 742 fraternities, there was only

one example of consanguinity (a first-cousin marriage with two children not affected) giving a rate of 0.13 per cent.

Clearly we cannot attach much significance to differences of this order based on records of a few hundred families. In any case we are unlikely to get much help from a study of consanguinity with a condition whose incidence is almost 0.6 per cent. As Hogben (1939) has indicated, where a recessive condition is rare, a high proportion of affected individuals are offspring of near relatives; but where it is common (more frequent than 0.2 per cent.) high rates of consanguinity will not be expected. The literature on malformations contains few reports of the incidence of consanguinity of parents, and none in which the incidence is known for the population from which cases were drawn. Malpas (1937) sent questionnaires to parents of 294 malformations, and recorded no example of consanguinity from 109 replies. Hindse-Nielsen (1938) found three consanguineous marriages among 124 couples who had offspring exhibiting spina bifida, and Murphy reported two first-cousin unions and one of second cousins among 553 couples observed by him. It may be noted that the incidence of first-cousin marriages shown above for parents of malformations and controls is lower than has usually been recorded for the general population. Elderton (1911) gave a figure of 3 per cent.; Hogben (1931) suggested that it varied between 0.5 and 1 per cent., but emphasized the uneven distribution in different sections of the community. There is some evidence (Bell, 1940) that the incidence of consanguinity is falling.

(d) *Rhesus Incompatibility*.—It was suggested by Wiener (1946) that at least one variety of spina bifida is produced by Rh sensitization. In support of this view he mentioned three families with erythroblastotic infants which also produced stillbirths with spina bifida, and quoted the experience of L. H. Snyder (unpublished) who observed three Rh-negative mothers (two of them exhibiting Rh antibodies), each of whom produced infants with spina bifida in her first two pregnancies. It is well known that a rhesus incompatibility is rarely present in a first pregnancy, so that the increased predisposition of the first-born to spina bifida (see Part I) could hardly be attributed to this cause. In any case it is not easy to accept the view that a serum incompatibility which affects the nutrition of the embryo in the third week is compatible with its continued development to a viable stage.

Although a number of our cases occurred prior to the discovery of the rhesus factor, or before its importance was generally appreciated, some of the more recent ones were born in hospitals well equipped for haematological investigations which have now become a routine procedure. In no case of spina bifida or other central nervous malformation was the presence of rhesus incompatibility noted. A conclusive answer would require the haematological investigation of an adequate number of malformations and their mothers and of a representative control group. In the absence of more suggestive evidence than is yet available, Wiener's results may reasonably be regarded as a fortuitous coincidence of two conditions neither of which is uncommon.

3. SUMMARY

Information obtained by home visits from 742 mothers of 755 malformations of the central nervous system is compared with that obtained from 742 mothers of 757 births not resulting in malformations. The results are as follows:

(1) Reproductive history of the mother.

(a) Menstruation. There are no appreciable differences in age at onset, length of cycle, or duration of flow between the mothers in the two groups.

(b) Age at marriage. Women who give birth to central nervous malformations are on the average a little older than other women when they marry.

(c) Results of other pregnancies. The abortion rate is much higher for sibs of the malformations than for sibs of controls; the stillbirth rate is higher for sibs of two malformations (anencephalus and hydrocephalus, but not spina bifida); infant mortality rates are not affected. The rate of foetal and infant loss is slightly increased by standardization for parity. The conception immediately prior to the malformation experiences a greater loss than the others, because of higher rates of infant mortality and abortion.

(d) Lactation. There is no significant difference in the proportions breast-fed between sibs preceding malformed births and sibs preceding control births.

(e) Fertility. There is little in the data to suggest that women who give birth to malformations are less fertile than other women, or that malformations arise when births succeed each other too rapidly. There is some evidence, especially in the case of hydrocephalus, that women are slightly less fertile in the period preceding the birth of a malformation than in that preceding their other conceptions.

(2) Familial incidence of malformations of the central nervous system.

(a) The incidence of malformations of the central nervous system in all notified births (live born and stillborn) is 0.59 per cent. The incidence in *all* sibs of a malformed propositus is 1.89 per cent. and that in sibs born *after* a malformed propositus is 5.18 per cent. Thus the risk for any birth following the malformation is almost nine times as great as the average risk.

(b) The risk of another malformation is relatively greatest when the first is spina bifida.

(c) In each of the three main central nervous malformations, the risk of recurrence of the same malformation is greater than the risk of a different one, but the risk of a different one is greater than that to which the general population of mothers is exposed.

(d) Other major malformations not involving the nervous system are not more common among sibs of malformations than among sibs of controls.

(e) Malformations, and particularly those of the nervous system, are more common among other relatives (sibs excluded) of fraternities which include central nervous malformations.

(f) There were three first-cousin marriages and one of second cousins among parents of 742 fraternities of malformations; there was one first-cousin marriage among parents of 742 fraternities of controls. The investigation of consanguinity for a condition as common as a central nervous malformation is in any case unlikely to be fruitful.

(g) No case of rhesus incompatibility was recorded, but many of the births occurred in years prior to the use of the requisite investigation. There are, however, grounds for doubting the aetiological importance of this factor.

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APPENDIX A

DETAILS OF FRATERNITIES CONTAINING TWO OR MORE MALFORMED OFFSPRING

Group I.—Fraternities in which all Malformations are Propositi of the present Series.

Fraternity	Birth Rank	Date of Birth	Result
a	1	1941	Miscarriage
	2*	Oct., '43	Stillbirth—spina bifida, hydrocephalus, and talipes
	3*	March, '45	Death at 13 days—spina bifida
b	1	Jan., '31	Live birth
	2	1932	Miscarriage
	3	Aug., '33	Live birth
	4	?	Miscarriage
	5	?	Miscarriage
	6*	July, '42	Stillbirth—spina bifida
	7*	Sept., '43	Death at 5 weeks—spina bifida
	8	?	Miscarriage
	9	April, '47	Live birth
c	1	Oct., '31	Live birth
	2	Dec., '35	Stillbirth—cause not known
	3	Feb., '38	Live birth. Died at 2 years—broncho-pneumonia
	4*	July, '41	Stillbirth—anencephalus
	5	?	Miscarriage
	6*	Nov., '43	Stillbirth—anencephalus
d	1	July, '40	Live birth
	2*	Sept., '41	Stillbirth—anencephalus
	3*	Oct., '42	Death at 8 hours—spina bifida and hydrocephalus
	4	June, '44	Live birth
	5	July, '48	Live birth
e	1	May, '36	Live birth
	2	Sept., '42	Miscarriage
	3*	Feb., '43	Stillbirth—anencephalus and spina bifida
	4*	Aug., '44	Death at 1 day—spina bifida, hydrocephalus, and talipes
	5	July, '47	Live birth
f	1*	Jan., '41	Death at 7 days—spina bifida
	2	Nov., '46	Live birth
	3*	Sept., '47	Stillbirth—spina bifida and encephalocele
g	1*	July, '45	Death at 6 months—hydrocephalus
	2*	Aug., '47	Death at 14 days—spina bifida
h	1*	Aug., '40	Death at 18 days—spina bifida
	2*	Sept., '42	Death at 1 month—spina bifida
i	1	Sept., '39	Live birth
	2*	Nov., '42	Death at 2 months—spina bifida
	3	Dec., '43	Live birth
	4*	Sept., '45	Stillbirth—anencephalus
	5*	March, '47	Death at 4 days—spina bifida and hydrocephalus
j	1	May, '36	Death at 10 hours—cause unknown
	2*	June, '42	Stillbirth—spina bifida and hydrocephalus
	3*	Dec., '43	Stillbirth—anencephalus and central placenta praevia

* Propositi, i.e. central nervous malformations, included in the present series.

Group I.—continued.

Fraternity	Birth Rank	Date of Birth	Result
k	1*	April, '41	Death at 3 months—spina bifida
	2*	April, '42	Death at 10 days—spina bifida
	3	Nov., '44	Live birth
	4	March, '47	Live birth
	5	Feb., '48	Miscarriage
l	1	Feb., '42	Miscarriage
	2	June, '43	Live birth
	3*	Dec., '47	Death at 1 day—hydrocephalus
	3* }		Death at 1 day—hydrocephalus }

Group II.—Fraternities in which only one Malformation is a Propositus of the present Series but which also contain an Individual with a Lethal Central Nervous Malformation.

a	1	March, '33	Stillbirth—placenta praevia
	2†	Feb., '34	Stillbirth—spina bifida
	3	March, '35	Live birth
	4	May, '36	Live birth
	5	Oct., '39	Live birth
	6	Oct., '40	Live birth
	7*	April, '42	Stillbirth—anencephalus
	8	Nov., '43	Live birth
b	1†	March, '41	Death at 5½ months—developmental defect of brain and malformation of lungs
	2*	June, '43	Death at 9 months—developmental defect of brain
	3	Oct., '45	Death at 4 months—cause unknown
	4	1946	Miscarriage
c	1†	Sept., '40	Stillbirth—anencephalus
	2	Feb., '42	Miscarriage
	3	June, '43	Miscarriage
	4	Aug., '44	Live birth
	5*	Dec., '47	Stillbirth—anencephalus
d	1†	June, '34	Death at 8 days—spina bifida
	2	Dec., '35	Live birth
	3	Aug., '38	Live birth
	4*	May, '43	Death at 9 weeks—spina bifida and hydrocephalus
e	1†	April, '35	Stillbirth—spina bifida
	2	May, '36	Live birth
	3	July, '38	Live birth
	4	1939	Miscarriage—multiple congenital abnormalities
	5	Oct., '41	Live birth
	6*	Aug., '44	Stillbirth—spina bifida and hydrocephalus
f	1	March, '38	Live birth
	2	Feb., '39	Miscarriage
	3	Feb., '43	Live birth
	4†	June, '44	Death at 1 week—spina bifida and deformity of hands
	5*	Sept., '47	Death at 2 days—hydrocephalus and congenital deformity of heart

* Propositi, i.e. central nervous malformations, included in the present series.

† Cases of stillbirth or infant death due to central nervous malformations not included in the present series.

Group II.—continued.

Fraternity	Birth Rank	Date of Birth	Result
g	1	Aug., '30	Live birth
	2	Feb., '32	Live birth
	3	July, '34	Live birth
	4†	July, '37	Death at 9 days—spina bifida
	5	July, '38	Live birth
	6*	Sept., '40	Stillbirth—anencephalus and spina bifida
	7	Aug., '46	Live birth
h	1	June, '31	Live birth
	2	Nov., '33	Live birth
	3†	May, '35	Stillbirth—spina bifida
	4	June, '37	Live birth
	5	Sept., '38	Live birth
	6	Nov., '40	Stillbirth—cause unknown
	7	Feb., '42	Live birth
	8	April, '43	Death at 6 days—accidental suffocation
	9*	April, '44	Stillbirth—anencephalus
	10	July, '45	Live birth
	11	April, '47	Live birth
i	1†	Feb., '31	Death at 5 days—spina bifida
	2	May, '32	Live birth
	3	Dec., '33	Live birth
	4*	Feb., '40	Stillbirth—anencephalus
j	1	Aug., '36	Live birth
	2	Nov., '38	{ Live birth
	2†		{ Stillbirth—hydrocephalus
	3	July, '41	{ Live birth
	3*		{ Stillbirth—hydrocephalus
	4	Oct., '44	Live birth
k	1	Jan., '30	Death at 1 month—cause unknown
	2	March, '31	Live birth
	3	May, '33	Live birth
	4	Feb., '37	Live birth
	5†	April, '39	Stillbirth—spina bifida
	6	Oct., '40	Live birth
	7	Jan., '42	Live birth
	8*	Sept., '43	Death at 1 week—spina bifida
	9	Feb., '45	Live birth
	10	May, '47	Live birth
l	1†	Jan., '38	Stillbirth—hydrocephalus
	2*	Nov., '40	Stillbirth—anencephalus
m	1†	May, '37	Death at 3 weeks—spina bifida
	2	Dec., '38	Miscarriage
	3*	March, '40	Stillbirth—anencephalus
	4	July, '43	Live birth
	5	Feb., '45	Live birth
n	1	Dec., '35	Live birth
	2	April, '40	Death at 2 months—pneumonia
	3	Oct., '41	Live birth
	4*	Sept., '43	Stillbirth—anencephalus
	5†	July, '46	Stillbirth—anencephalus

* Propositi, i.e. central nervous malformations, included in the present series.

† Cases of stillbirth or infant death due to central nervous malformations not included in the present series.

Group II.—continued.

Fraternity	Birth Rank	Date of Birth	Result
o	1†	Nov., '39	Stillbirth—spina bifida and hydrocephalus
	2*	April, '46	Stillbirth—spina bifida and hydrocephalus
	3	Nov., '47	Live birth
p	1†	Aug., '38	Stillbirth—anencephalus
	2*	March, '44	Stillbirth—hydrocephalus

Group III.—Fraternities in which only one Malformation is a Propositus of the present Series, but which also contain an Individual with either a Non-lethal Central Nervous Malformation or a Malformation of another System.

a	1*	June, '43	Stillbirth—anencephalus
	2	1944	Live birth—mild degree of spina bifida successfully treated by surgery
	3	1947	Live birth
b	1	Sept., '19	Live birth
	2	Dec., '20	Live birth
	3	May, '23	Live birth
	4	July, '35	Live birth—talipes. Still alive
	5	Nov., '39	Stillbirth—cause unknown
	6*	Nov., '42	Stillbirth—anencephalus
c	1	Sept., '44	Live birth—pyloric stenosis successfully treated
	2*	Dec., '45	Stillbirth—hydrocephalus
d	1	Sept., '42	Live birth
	2*	Jan., '45	Death at 7 days—spina bifida
	3	Aug., '46	Live birth—hydrocephalus. Still alive 2 years later
e	1	Oct., '33	Live birth
	2	Feb., '35	Live birth
	3	July, '37	Live birth
	4	Dec., '38	Live birth
	5	Oct., '39	Stillbirth—cause unknown; imperforate anus present
	6	March, '41	Live birth
	7	March, '42	Live birth
	8	June, '44	Live birth
	9*	Feb., '46	Death at 1 hour—spina bifida
f	1	Nov., '42	Live birth
	2*	Oct., '44	Death at 14 days—occipital meningocele
	3	Feb., '47	Death at 19 hours—congenital defect of heart

* Propositi, i.e. central nervous malformations, included in the present series.

† Cases of stillbirth or infant death due to central nervous malformations not included in the present series.

APPENDIX B

DETAILS OF FRATERNITIES IN THE CONTROL GROUP CONTAINING MALFORMED OFFSPRING

Fraternity	Birth Rank	Date of Birth	Result
a	1	Dec., '32	Death at 1½ years—cerebral tumour
	2	Jan., '34	Live birth
	3	Aug., '39	Live birth
	4*	Aug., '43	Live birth—webbed fingers
	5	April, '47	Live birth
b	1	May, '42	Live birth
	2*	May, '46	Live birth—congenital cataract (familial)
c	1*	Feb., '43	Live birth
	2	April, '44	Miscarriage
	3	Oct., '44	Miscarriage
	4	Sept., '45	Live birth
	5†	May, '47	Stillbirth—monster, hydrops foetalis
d	1*	Jan., '47	Live birth
	2†	March, '48	Live birth—pyloric stenosis successfully treated
e	1†	Sept., '41	Stillbirth—gross deformities
	2*	April, '43	Live birth
f	1	Oct., '37	Live birth
	2*	May, '40	Live birth
	3	June, '42	Live birth
	4†	July, '44	Death at 3½ months—gastro-enteritis following surgical treatment of hare-lip
g	1†	Dec., '40	Death at 12 days—spina bifida
	2	April, '44	Live birth
	3*	Dec., '47	Live birth
h	1†	Feb., '32	Live birth—imperforate anus successfully treated
	2	Aug., '37	Live birth
	3*	Jan., '40	Live birth
	4	April, '44	Live birth
i	1†	Jan., '41	Death at 18 days—congenital cardiac defect
	2	Feb., '43	Live birth
	3*	July, '44	Live birth
	4	June, '47	Miscarriage
j	1	Nov., '35	Live birth
	2†	Feb., '39	Death at 2 months—spina bifida
	3*	June, '41	Live birth
	4	Dec., '45	Live birth
k	1†	Oct., '39	Stillbirth—cerebral deformity
	2	April, '42	Live birth
	3*	July, '46	Live birth
l	1	Sept., '40	Live birth
	2†	March, '44	Stillbirth—anencephalus
	3*	Oct., '47	Live birth

* Propositi.

† Non-lethal malformations occurring among sibs of propositi.

‡ Lethal malformations occurring among sibs of propositi.

Control Group.—continued.

Fraternity	Birth Rank	Date of Birth	Result
m	1	Oct., '30	Live birth
	2	Oct., '34	Live birth
	3†	Dec., '38	Live birth—webbed toes of both feet
	4*	Aug., '47	Live birth
n	1	Jan., '29	Live birth
	2	Jan., '32	Stillbirth—asphyxia
	3†	Feb., '34	Live birth—webbed toes of left foot
	4*	Oct., '43	Live birth
	5	July, '45	Live birth
o	1†	Dec., '36	Death at 4 days—tracheo-oesophageal fistula
	2	Aug., '42	Miscarriage
	3	Aug., '44	Live birth
	4*	March, '46	Live birth
p	1†	April, '37	Death at 5 weeks—pyloric stenosis
	2	Jan., '41	Live birth
	3	Dec., '46	Live birth
	4* }	Dec., '47	Live birth
	4* }		Death at 7 weeks—cause unknown
q	1†	Nov., '33	Death at 2 days—malformation (unspecified type)
	2	Nov., '34	Miscarriage
	3	June, '36	Live birth
	4	Feb., '38	Live birth
	5	July, '39	Death at 4 months—gastro-enteritis
	6*	Feb., '44	Live birth
	7	Jan., '47	Live birth

* Propositi.

† Non-lethal malformations occurring among sibs of proposti.

‡ Lethal malformations occurring among sibs of proposti.