

CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM III.—RISK OF MALFORMATION IN SIBS OF MALFORMED INDIVIDUALS

BY

R. G. RECORD and THOMAS McKEOWN

From the Department of Social Medicine, University of Birmingham

Using data for the City of Birmingham, we previously estimated the incidence of malformations of the central nervous system in sibs born after a first malformed propositus as 5·18 per cent., about nine times the incidence (0·59 per cent.) in all notified births (Record and McKeown, 1950). In arriving at this estimate we included fraternities of two kinds:

- (a) those in which the first malformed individual was born within the period covered by the survey (1940-47),
- (b) those in which the first malformed individual was born before 1940.

Fraternities under (b) are clearly unrepresentative, since they come to our attention only because a second or later malformation has occurred in the years 1940-47*; and consequently the estimate of the risk to sibs is too high when they are included. We have therefore recalculated the incidence by confining our attention to fraternities under (a), and have taken the opportunity to consider more carefully the validity of a comparison with the incidence in all notified births.

TABLE I

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

Type of First Malformation	Anen- cephalus	Spina bifida	Hydro- cephalus	Other	Total
Sibs born after the first malformation	190	205	61	14	470
Number of malformations	4	8	1	0	13
Malformation rate (per cent.)	2·1	3·9	1·6	—	2·77

* This table is based on 727 fraternities in which the first malformation occurred in the period 1940-47.

The previous estimate of the incidence in sibs (5·18 per cent.) was based on 742 fraternities, of which fifteen are now excluded because the first malformation occurred before 1940 (twelve cases) or outside Birmingham (three cases). In the remaining 727 fraternities there were thirteen malformations in 470 sibs (2·77 per cent.). This estimate is based only on sibs born after the first malformation and before the end of 1947 (Table I).

* We are greatly indebted to Dr. C. O. Carter for having brought this point to our attention.

TABLE II
DISTRIBUTIONS BY MATERNAL AGE AND PARITY OF 755 MALFORMATIONS AND OF 742 CONTROL BIRTHS

Maternal Age	Parity										Totals	
	1		2		3 and 4		5 and 6		7 and over			
	Malformations	Controls	Malformations	Controls	Malformations	Controls	Malformations	Controls	Malformations	Controls	Malformations	Controls
17-26	208	163	58	82	32	42	4	2	—	—	302	289
27-36	115	82	102	125	84	112	30	36	10	8	341	363
37-46	11	7	13	14	28	31	22	23	38	15	112	90
Totals	334	252	173	221	144	185	56	61	48	23	755	742

The incidence of malformations in sibs (2.77 per cent.) cannot fairly be compared with the incidence in all births (0.59 per cent.) since the age and parity

TABL
ESTIMATED DISTRIBUTIONS BY MATERNAL AGE AND PARITY

Maternal Age	Par								
	1			2			3 and 4		
	Malformations	Total births	Percentage malformed	Malformations	Total births	Percentage malformed	Malformations	Total births	Percentage malformed
17-26	256.2	34,776	0.737	71.4	17,495	0.408	39.4	8,961	0.440
27-36	141.7	17,495	0.810	125.6	26,669	0.471	103.5	23,895	0.433
37-46	13.5	1,493	0.904	16.0	2,987	0.536	34.5	6,614	0.522
Totals	411.4	53,764	0.765	213.0	47,151	0.452	177.4	39,470	0.449

* The known age and parity distributions of 755 malformations and of 742 controls (see Table II)

TABL
OBSERVED AND EXPECTED NUMBERS

Maternal Age	Par								
	2			3 and 4					
	No. of sibs	No. of sibs malformed		No. of sibs	No. of sibs malformed				
		Observed	Expected		Observed	Expected			
17-26	95	3	0.388	68	1	0.299			
27-36	74	0	0.349	134	4	0.580			
37-46	5	0	0.027	15	1	0.078			
Totals	174	3	0.764	217	6	0.957			

* Expected numbers of malformed sibs have been calculated by applying the rates for each age and parity group given in Table III to the number of sibs at risk.

MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM—III 219

distributions of the 470 sibs (upon which the estimate is based) are quite unrepresentative. For example, they exclude all first births, with which increased risks of malformation are associated. Taking account of variation in the risk associated with maternal age and parity in the general population of births, an expected incidence of malformations among the sibs of 0.50 per cent., is obtained thus:

- (i) by using the known age and parity distributions of 755 malformations and of 742 control births (Table II) to give distributions for 930 malformations and 158,307* total births,
- (ii) by calculating malformation rates for each group (Table III),
- (iii) by using these rates to give expected numbers of malformations among sibs in each age and parity group (Table IV).

This rather elaborate treatment uses information about the malformation rates in all age and parity groups to give an expected incidence for the 470 sibs. The

* These are the observed numbers of malformations of the central nervous system (live born and stillborn), and of related total births born in Birmingham, in the period covered by the investigation (1940-47).

E III
OF 930 MALFORMATIONS AND OF 158,307 TOTAL BIRTHS*

ity

5 and 6			7 and over			Totals		
Malformations	Total births	Percentage mal-formed	Malformations	Total births	Percentage mal-formed	Malformations	Total births	Percentage mal-formed
4.9	427	1.148	—	—	—	371.9	61,659	0.603
37.0	7,681	0.482	12.3	1,707	0.721	420.1	77,447	0.542
27.1	4,907	0.552	46.8	3,200	1.463	137.9	19,201	0.718
69.0	13,015	0.530	59.1	4,907	1.204	929.9	158,307	0.587

are here applied to 930 malformations and to 158,307 total births.

E IV
OF MALFORMATIONS AMONG SIBS*†

ity

5 and 6			7 and over			Totals		
No. of sibs	No. of sibs malformed		No. of sibs	No. of sibs malformed		No. of sibs	No. of sibs malformed	
	Observed	Expected		Observed	Expected		Observed	Expected
3	1	0.034	0	0	—	166	5	0.721
29	1	0.140	14	0	0.101	251	5	1.170
13	1	0.072	20	1	0.293	53	3	0.470
45	3	0.246	34	1	0.394	470	13	2.361

† Incidence of malformations among sibs: Expected = $\frac{2.361}{470} \times 100 = 0.50\%$. Observed = 2.77%.

same result (0.50 per cent.) is obtained more readily by estimating an expected incidence of malformations in birth ranks two and higher. This suggests, as might be expected, that it is mainly because they exclude all first births that the sibs cannot be compared with the general population of births.

TABLE V
EXPECTED NUMBERS OF MALFORMATIONS IN SIBS CALCULATED FROM ANNUAL MALFORMATION RATES FOR BIRTH RANKS TWO AND HIGHER*

Year	1940	1941	1942	1943	1944	1945	1946	1947	Totals
Number of sibs	0	9	28	59	78	87	88	121	470
Estimated malformation rates for birth ranks 2 and higher†	0.76	0.51	0.60	0.58	0.40	0.43	0.45	0.40	—
Expected number of malformations	0	0.05	0.17	0.34	0.31	0.37	0.40	0.48	2.12

* Expected incidence of malformations among sibs = $\frac{2.12}{470} \times 100 = 0.45$ per cent.

† Annual numbers in birth ranks two and higher (from which rates are calculated) obtained thus:
(a) Malformations: The data available for 755 malformations are applied to 930 malformations.
(b) Controls: The data available for 742 controls are applied to 158,307 total births.

We should also note that sibs were not distributed evenly between the eight years (1940-47), and this fact assumes importance because of evidence of a secular trend in the malformation rate (Record and McKeown, 1949). We have therefore thought it necessary to calculate an expected number of malformations by applying estimated annual malformation rates for birth ranks two and higher to the number of sibs born in each year (Table V). The expected incidence obtained in this way is 0.45 per cent., and since this figure takes account of both parity and secular trend it is considered most suitable for comparison with the observed incidence of malformations in the 470 sibs (2.77 per cent.). The observed incidence is thus approximately six times the expected incidence.

SUMMARY

The observed incidence of malformations of the central nervous system in sibs born after a first propositus was 2.77 per cent. This is approximately six times the expected incidence of 0.45 per cent. In estimating the expected incidence, we have taken account of the secular trend of the malformation rate in Birmingham in the years 1940-47, as well as of variations in the rate associated with maternal age and parity.

REFERENCES

- Record, R. G., and McKeown, T. (1949). *British Journal of Social Medicine*, 3, 183.
——— (1950). *Ibid.*, 4, 26.