Brit. J. prev. soc. Med. (1964), **18**, 98–101

AN EXAMINATION OF FAMILIAL DATA FOR ASSOCIATED BIRTH-ORDER EFFECTS IN THE PRESENCE OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

BY

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INTRODUCTION

A number of investigations have been made of the estimation of the incidence of central nervous system (CNS) malformations. Several of these studies (*e.g.* McKeown and Record, Ciba Foundation, 1960) have stressed the association of malformations (e.g. spina bifida with anencephalus or hydrocephalus). The possible effects of birth order upon these malformations have been commented upon by several authors, but the conclusions seem to vary according to the author. Thus Record and McKeown (1949), on the basis of their examination of 930 cases of malformations in Birmingham, considered that the risk of a CNS malformation increased considerably at the first parity and beyond the sixth, but was approximately constant in the interval. These authors stated that maternal age did not appear to be associated with the incidence of malformations. On the other hand, Ingalls, Pugh, and McMahon (1954), in their study of Rhode Island hospital data, stated that for anencephalus and spina bifida the incidence appeared to drop from the first to the second parity, but then increased with subsequent sibs. The analysis of Scottish data by Edwards (1958) suggests an increased risk in primogeniture for anencephalus but further analysis for spina bifida and hydrocephalus was not done in view of limited data.

It is of interest therefore to examine systematically certain available series of family data for the occurrence of possibly significant birth-order effects, especially when two or more sibs were affected with various CNS malformations.

The familial data examined using a common classification of CNS malformations are set out in Table I:

TABLE I

FAMILIAL DATA EXAMINED ON CNS MALFORMATIONS

Author	Date	No. of Families
Böök and Rayner	1950	46
Labrum and Wood	1961	10
MacMahon, Pugh, and Ingalls	1953	49
Milham	1962	10
Penrose	1946	137
Polman	1950	181

The following categories were used in the statistical analysis:

Category No.	*Definition*	*Category No.*	*Definition*
1	Anencephalus	6	Normal
2	Anencephalus with Spina Bifida	7	Abortion, Stillbirth, Miscarriage, Premature, +Infant Deaths
3	Spina Bifida	8	Mental Deficiency or Epilepsy
4	Spina Bifida and Hydrocephalus or Microcephalus	9	Other Defects
5	Hydrocephalus or Microcephalus		

Bennett (1963) has proposed a simple statistical test in examining familial data with respect to possibly significant birth-order effect in the several categories. It is a conditional statistical test in the

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sense that each group of specified categories (*e.g.* abnormalities) is known to have a fixed number of members, and that it then ascertains whether there are significant deviations from randomness in the occurrence of the successive members in the groups.

Statistical Test for Birth-Order Effect

Suppose that a single sibship, consisting of n sibs without missing ones or twins, is grouped according as each successive sib may be classified in one and only one of c mutually exclusive categories E_1, E_2, . . . , E_c of abnormalities including "Normal". For example, if $c=3$, the categories may be E_1: "Anencephalus", E_2: "Anencephalus with Spina Bifida", E_3: "Normal".

For each category, call X_i ($i=1, \ldots, c$) the sum of the birth orders $=\Sigma x_{ij}$ of the affected sibs in category E_i, and n_i the number of sibs observed in this category ($n=\Sigma n_i$). Then the test

$$\chi^2 = \frac{12}{n\,(n+1)} \sum_{i=1}^{c} \frac{1}{n_i} [X_i - \tfrac{1}{2}(n+1)\, n_i]^2$$

$$= \frac{12}{n\,(n+1)} \left(\sum \frac{1}{n_i} X_i^2\right) - 3\,(n+1) \qquad (1)$$

has approximately the χ^2—distribution with $(c-1)$ degrees of freedom. It suffices to consider only $(c-1)$ of the X's, since

$$X_c = \tfrac{1}{2}\, n\,(n+1) - \left(\sum_{i=1}^{c-1} X_i\right)$$

If there are only two categories (*e.g.* "Affected" and "Normal"), the test above reduces to that proposed by Haldane and Smith (1948).

As an example of the use of this test, consider the following data of Milham (1962), where the presence or absence of each of the specified conditions is denoted by a 1 or 0, respectively:

Table II

DATA FOR PATIENT No. 3 (MILHAM, 1962)

Pregnancy No.	Anencephalus	Premature or Abortion	Normal
1	0	1	0
2	0	0	1
3	0	0	1
4	1	0	0
5	0	0	1
6	0	0	1
7	0	0	1
8	0	0	1
9	1	0	0
10	1	0	0
Total ..	$X_1=23$	$X_2=1$	$X_3=31$

In this way the test (1) becomes

$$\chi^2 = \frac{12}{n\,(n+1)} \left[\frac{1}{3}(23)^2 + (1)^2 + \frac{1}{6}(31)^2\right]$$

$$- 3\,(10+1) = 3{\cdot}82,$$

for which P ($\chi^2 \geqslant 3{\cdot}82$) = ·15, and hence there is little evidence of a significant birth-order effect amongst the successive pregnancies.

In connexion with the use of the test (1) in the analysis of variance of continuous data, Kruskal and Wallis (1952, 1953) tabulated the exact distribution of the X's for $c=3$ and values of n up to 5.

The χ^2 test has therefore been systematically applied to the family data listed in Table I. Certain families were omitted:

(*i*) When there were twins or missing sibs,

(*ii*) When the exact classification or category could not be ascertained from the author's list,

(*iii*) When the number of categories equalled the number of sibs ($n=c$).

The situation $n=c$ is omitted, since in this case $\chi^2=(c-1)$ for $(c-1)$ degrees of freedom, and the resulting probability approaches 0·5.

The resulting individual and combined χ^2 values have been provided for each of the appropriate groupings of categories, and a detailed summary is given in the Appendix Table (overleaf). It may be noted that in no instance was any statistically significant result found, so that based on these family data there is little evidence of any significant birth-order effect on CNS malformations.

Although the overall χ^2 values are not significant for the complete group of categories, in these families it might be inquired whether any sub-groupings of these categories could still show a statistically significant result for the same families. This has been investigated by computing the components of the χ^2 values in those families where certain small (though insignificant) probabilities were obtained. No significant results were noted.

Finally, it should be mentioned that the use of test (1) may be considered mainly effective in the detection of some "trend" (*e.g.* linear) in birth-order effect, *i.e.* whether there is a directly increasing or decreasing chance of the occurrence of particular defects amongst the successive sibs of the families in which these defects were noted. If, for example, periodicity in birth-order effect is of concern, test (1) could not be considered very effective in its detection.

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SUMMARY

This paper examines some principal series of familial data in which at least one sib had one or more malformations of the central nervous system with respect to testing whether there are significant birth-order effects. For this purpose, a χ^2 test proposed earlier by Bennett (1963) is used in examining the sibships. No statistically significant birth-order effects were found by this analysis.

The authors would like to acknowledge the counsel of Drs E. R. Alexander and I. Emanuel of the Department of Preventive Medicine on some of the medical aspects of the CNS familial data, and also certain financial support from the State of Washington Initiative 171 Fund for Research in Biology and Medicine.

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Appendix Table
Detailed Analysis of Family Data

Author and Date	Categories	No. of Families	No. of Sibs	Combined χ^2	D.F.	Probability
Böök and Rayner (1950)	1,6	11	45	12·54	11	·33
	2,6	3	9	4·50	3	·21
	1,6,7	7	42	16·79	14	·27
	1,6,8	1	5	2·13	2	·35
	2,6,7	1	6	3·57	2	·17
	2,6,8	1	4	2·70	2	·26
	2,3,6	1	5	3·20	2	·20
		25	116	45·43	36	·14
	Not Considered	21				
	Total Cases	46				
Labrum and Wood (1961)	1,7	1	3	0·00	1	·99
	5,6	1	4	2·40	1	·12
	5,9	2	6	3·00	2	·22
		4	13	5·40	4	·25
	Not Considered	6				
	Total Cases	10				
MacMahon, Pugh, and Ingalls (1953)	1,6	1	4	0·60	1	·44
	2,6	1	8	1·00	1	·32
	3,6	1	3	0·00	1	·99
	4,6	2	7	2·10	2	·35
	5,9	1	3	1·50	1	·22
	1,2,6	1	12	4·65	2	·10
	1,3,6	5	29	8·16	10	·61
	1,4,6	2	10	5·33	4	·25
	1,5,6	1	8	0·53	2	·77
	1,6,7	1	7	1·25	2	·53
	1,6,9	2	10	6·40	4	·17
	2,3,7	1	4	2·70	2	·26
	3,4,6	3	14	7·00	6	·32
	3,5,6	1	6	2·50	2	·29
	3,6,7	1	4	2·70	2	·26
	3,6,9	2	8	5·40	4	·25
	4,6,7	1	4	2·70	2	·26
	1,2,6,7	1	5	3·20	3	·36
	1,3,5,6	1	6	3·67	3	·29
	1,4,6,7	1	5	0·80	3	·85
	2,3,6,7	1	6	4·43	3	·22
	3,4,6,7,9	1	11	3·97	4	·41
		32	174	70·59	64	·27
	Not Considered	17				
	Total Cases	49				
Milham (1962)	1,6	1	3	1·50	1	·22
	3,6	1	5	0·33	1	·57
	1,3,6	2	11	4·11	4	·39
	1,6,7	1	10	3·82	2	·15
	1,3,6,7	2	13	3·75	6	·71
		7	42	13·51	14	·49
	Not Considered	3				
	Total Cases	10				
Penrose (1946, 1957)	1,6	3	11	1·33	3	·72
	2,6	1	3	1·50	1	·22
	3,6	14	65	21·26	14	·10
	4,6	6	30	7·15	6	·30
	5,6	7	32	8·12	7	·32
	3,7	1	3	1·50	1	·22
	1,6,7	2	11	5·65	4	·23
	1,6,8	1	6	3·57	2	·17
	3,6,7	7	45	18·67	14	·18
	3,6,8	2	10	3·74	4	·44
	3,6,9	2	12	5·81	4	·21
	3,4,6	1	4	0·30	2	·86
	4,6,7	2	13	4·73	4	·32
	5,6,7	10	72	22·31	20	·32
	5,6,8	4	31	8·29	8	·41
	1,3,6,7	2	13	7·09	6	·31
	1,6,7,8	1	10	5·94	3	·11
	3,6,7,8	2	22	6·18	6	·40
	3,6,7,9	1	9	2·77	3	·42
	4,6,7,8	2	15	7·12	6	·31
	5,6,7,8	2	26	2·42	6	·88
	5,6,7,9	1	5	0·80	3	·85
	3,6,7,8,9	1	9	3·37	4	·49
		75	457	149·62	131	·13
	Not Considered	62				
	Total Cases	137				
Polman (1950)	1,6	49	229	56·05	49	·23
	2,6	4	18	4·34	4	·36
	3,6	18	102	23·29	18	·18
	4,6	7	33	8·30	7	·31
	5,6	6	30	6·07	6	·42
	1,3,6	6	31	8·75	12	·72
	1,5,6	2	16	6·60	4	·16
	1,6,7	11	81	24·38	22	·33
	2,6,7	3	12	7·20	6	·30
	3,4,6	1	5	3·00	2	·22
	3,6,7	2	12	4·65	4	·33
	4,6,7	2	11	5·70	4	·22
	1,3,6,7	2	27	3·86	6	·70
	1,5,6,7	1	9	0·36	3	·95
		114	616	162·55	147	·18
	Not Considered	67				
	Total Cases	181				

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