THE FAMILIAL INCIDENCE OF CONGENITAL MALFORMATION OF THE HEART

BY

THOMAS MCKEOWN, BRIAN MACMAHON,* AND C. G. PARSONS

*From the Department of Social Medicine, University of Birmingham,
and the Children's Hospital, Birmingham*

Received October 23, 1952

It is generally believed that the incidence of congenital malformation of the heart is raised in relatives of affected individuals. The evidence in support of this view consists mainly of isolated records of families with more than one affected member (Courter *et al.*, 1948, refer to 63 reported cases), but a few examples have been noted in the course of investigations of large series of patients (for example, by Abbott, 1927; Dogramaci and Green, 1947; Campbell, 1949; and Lamy and Schweisguth, 1950, among others). Such observations are suggestive, but scarcely justify a confident assertion that incidence in relatives is raised, since both the numbers of relatives at risk and the incidence of affected in the related general populations were unknown. In the present communication we give the numbers of affected and unaffected relatives of a series of patients with various congenital cardiac malformations. All known affected relatives were recorded during the enquiry, but observations on incidence are restricted to brothers, sisters, parents, and first cousins of *propositi*. The data suggest that incidence of congenital malformation of the heart is raised in sibs, but is not raised in parents and cousins of affected individuals.

Material. We have previously described an investigation in which an attempt was made to record all cases of congenital malformation of the heart in children born to Birmingham mothers in the years 1940–49 (MacMahon *et al.*, 1953): 633 affected were identified in a population of 194,418 births, but for investigation of familial incidence we have used only 478 in which the diagnosis was confirmed post mortem (236), at operation (19), or clinically by a consultant physician (223); many of the cases were also investigated thoroughly. Of the 478 *propositi*, 431 (90%) drawn from 425 fraternities, were traced by field enquiry and family histories recorded. Where a history of congenital heart disease in a relative was elicited, the diagnosis was checked if possible by reference to hospital records or by examination by one of us (C.G.P.).

While accepting the diagnosis of congenital heart disease in all 431 *propositi* traced, we have accepted the diagnosis of the specific cardiac defect only in cases examined post mortem (206) or at operation (17).

INCIDENCE IN SIBS

In the 425 fraternities for which data are available there were 1012 sibs of the first *propositus* in each fraternity (that is of the first affected individual born in Birmingham in the period 1940–49); of these 646 were born before, 352 were born after, and 14 were twins of *propositi*. The incidence of malformations in sibs born before is of little interest, and we confine attention to the 352 sibs born after first *propositi*. They are derived from fraternities of two kinds: (a) 417 in which the

* In receipt of a grant from the Medical Research Council.

first malformed individual was a propositus; and (b) 8 in which the first malformed individual was not a propositus, being born before 1940. Fraternities under (b) are unrepresentative, since they come to attention only because a second malformation has occurred. It follows that if the likelihood of a third malformation in a fraternity is greater than of a second, the incidence in later sibs will be too high if they are included. We therefore restrict examination of incidence to the 417 fraternities under (a).

Table I shows that there were 6 affected among the 342 sibs born after the first propositus in 417 fraternities. This incidence (18 per 1000) is approximately six times that (3.2 per 1000) in the general population of births (MacMahon *et al.*, 1953). Table II gives details of the fraternities in which a later sib was affected. Five of the six sibs were propiti in the series; the sixth was

TABLE I
INCIDENCE OF CONGENITAL HEART DISEASE IN SIBS BORN AFTER THE
FIRST PROPOSITUS IN EACH FRATERNITY

First propiti		Subsequent sibs	
Nature of defect	Number	Number	Number with congenital heart disease
Transposition of the great vessels ..	28	24	1
Persistent common truncus arteriosus	15	17	0
Pulmonary stenosis	20	21	0
Coarctation of aorta	22	20	0
Septal defects	63	42	1
Patent ductus arteriosus	34	39	1
Other specified defects	33	26	0
Unspecified	202	153	3
Total	417	342	6

born in 1951, after the period covered by the enquiry. In three cases the diagnosis of congenital heart disease in the affected sib was confirmed post mortem; in the other three it rested on clinical examination (in one case accompanied by full investigation).

In three of the fraternities shown in Table II the specific nature of the cardiac defect was fairly reliably established in both affected: in two of them the first propositus and the affected sib exhibited the same abnormality (ventricular septal defect in one case, and complete transposition of the great vessels in the other). In the third fraternity the first propositus had a patent ductus arteriosus, and the sib showed transposition of the great vessels with ventricular septal defect. A specific congenital heart defect was also diagnosed in 2 of the 646 sibs born before the first propositus in each fraternity (both were born before the period of enquiry and are therefore not included among propiti). In one case the sib and propositus had a patent ductus arteriosus (both confirmed at operation): in the other the sib was examined clinically and thought to have a ventricular septal defect; the propositus exhibited Fallot's tetralogy (confirmed post mortem). Thus in three of five fraternities with two affected members in which the nature of the cardiac defect was known, the lesion was identical in both affected. The number of observations is of course very small, but this evidence suggests that the risk of recurrence of the same cardiac malformation may be greater than the risk of a different one.

The incidence of malformations other than congenital heart disease was not raised in sibs of propiti. Of the 1012 sibs, 9 exhibited other malformations, which were: anencephalus, spina bifida, harelip and cleft palate, absence of palate, aplasia of kidneys with talipes, absence of sternum,

TABLE II
DETAILS OF SIX FRATERNITIES IN WHICH A LATER SIB WAS AFFECTED

Birth rank	Sex	Date of birth	Fate	Diagnosis
1	M	20/4/40	Alive at 9 years	Unspecified cardiac defect (clinical examination) Fallot's tetralogy (full investigation)
2	F*	7/6/48	Died aged 3 weeks	
3	M*	20/6/49	Alive at 2 years	
1	F*	6/9/40	Died aged 7 weeks	Patent ductus arteriosus (P.M.) Unspecified cardiac defect (clinical examination) Cause of death unknown
2	F	31/12/42	Alive at 8 years	
3	F	12/1/44	Alive at 7 years	
4	M	20/1/45	Alive at 6 years	
5	M	10/10/46	Alive at 4 years	
6	F*	16/9/49	Died aged 3 months	
7	F	11/4/50	Died aged 2 days	
8	F	25/8/51	Alive at 5 weeks	
1	F*	7/5/42	Died aged 3 weeks	Unspecified cardiac defect (clinical examination) Patent ductus arteriosus (clinical examination)
2	F*	4/10/47	Alive at 4 years	
1	M*	30/1/43	Alive at 8 years	Patent ductus arteriosus (clinical examination) Transposition of great vessels and ventricular septal defect (P.M.)
2	F*	17/1/45	Died aged a few hours	
3	F (twin) M	17/1/45 10/6/50	Alive at 6 years Alive at 1 year	
1	F	6/4/45	Alive at 6 years	Ventricular septal defect and marked cardiac hypertrophy (P.M.) Ventricular septal defect (P.M.)
2	F*	14/1/48	Died aged 3 months	
3	F*	25/11/49	Died aged 7 days	
1	M	8/3/47	Died aged 3 days	Intracranial hæmorrhage (P.M.) Complete transposition of great vessels (P.M.) Complete transposition of great vessels (P.M.)
2	M*	12/11/49	Died aged a few hours	
3	M	10/6/51	Died aged 13 days	

* Propositus.

deaf mutism, Klippel Feil syndrome, and pseudo-hermaphroditism. This incidence (0.9%) is certainly no greater than that of malformations in the general population. It is of course possible that a few cases in stillbirths have been missed, but the number lost in this way must be small.

The mortality experienced by sibs appears not to have been raised. Among 997 sibs of propiti (excluding 15 confirmed or suspected cases of congenital heart disease from the original 1012) there were 32 stillbirths (32 per 1000 total births) and 51 infant deaths (53 per 1000 live births). The abortion rate experienced in the fraternities (propositi excluded) was 79 per thousand pregnancies. These rates are probably no higher than those prevailing in the general population of births during the same period.

It is unfortunately not possible to speak with confidence about the incidence of congenital heart disease in twins. There were 15 pairs of twins in the series, one with both members affected (both propiti), and 14 with one affected. But the 14 unaffected twins (of which 9 were alive at the time of investigation) were not examined, and the possibility that some of them were also affected cannot be excluded.

INCIDENCE IN COUSINS

Name and sex of all brothers and sisters of parents of propiti were recorded by field enquiry, as were the number and sex of their offspring. Suspected cases of congenital heart disease were noted. Fraternities (of first cousins of propiti) not well known to the person interviewed were excluded.

Of the 4143 cousins for whom a history was recorded, 25 were said to be affected. Inspection of hospital records confirmed the diagnosis in four cases, and refuted it in seven. Only one of the remaining 14 patients was available for clinical examination, and was found to be affected. It is of course quite possible that not all affected cousins were identified by relatives. But it seems certain that several of the 13 patients in whom the diagnosis was unconfirmed were unaffected, since of the 11 whose hospital records were traced, 7 were normal. Even if both confirmed (5) and unconfirmed (13) cases are included, the incidence in cousins (4.3 per 1000) is only a little higher than in the general population of births (3.2 per 1000).

INCIDENCE IN PARENTS

Data were recorded by field enquiry for 834 parents (424 mothers and 410 fathers). One mother refused to give the necessary information, and in 14 cases the child was illegitimate and the identity of the father unknown.

Fourteen parents were said to have congenital heart lesions. Twelve were examined clinically, when it was found that four had rheumatic heart disease and eight were normal. In the remaining two who were not examined the diagnosis had been made by a consultant physician and can probably be accepted: one of them (a mother) had a congenital heart block with some other lesion (probably a ventricular septal defect); and the other (a father) died of bacterial endocarditis with suspected congenital heart disease. In these two cases the specific nature of the defect in the propositus was not diagnosed. The incidence in parents (one or possibly two in 834) is possibly no higher than in the general population of adults, of which our only indication is the estimated incidence (1.1 per 1000) in children aged ten years (MacMahon *et al.*, 1953).

There were two first-cousin marriages (0.5%) among the 424 marriages of parents of propositi: in both cases the propositus exhibited dextrocardia and transposition of the viscera. There were seven patients with dextrocardia in the series, and the high incidence of consanguinity of parents in these cases provides support for Cockayne's suggestion (1938) that this condition may be inherited as a recessive.

There was one second-cousin marriage, which gave rise to a propositus with cor biloculare and atresia of the oesophagus.

SUMMARY

The familial incidence of congenital heart disease was recorded for 425 fraternities which contained 431 propositi born to Birmingham mothers in the years 1940-49. There were six affected (18 per 1000) among 342 sibs born after the first propositus. This is approximately six times the incidence (3.2 per 1000) in the general population of births. The incidence of malformations other than congenital heart disease was not raised in sibs of propositi.

The nature of the cardiac defects was fairly reliably diagnosed in five fraternities with two affected members; in three of them the lesions were identical in both affected.

Five confirmed and 13 unconfirmed cases of congenital malformation of the heart were identified among 4143 first cousins of propositi. Of 834 parents, 14 were said to be affected. Further clinical examination indicated that eight of them were normal, four had rheumatic heart disease, and only two had congenital heart lesions.

There were two first-cousin marriages among 424 marriages of parents of propositi; in both cases the propositus exhibited dextrocardia and transposition of the viscera. In the series there were seven propositi with dextrocardia, and the high incidence of consanguinity provides support for Cockayne's suggestion that this condition may be inherited as a recessive.

For clinical records we are indebted to the staffs of all Birmingham hospitals, in particular of the Children's Hospital, and for post-mortem reports to Dr. H. S. Baar, Dr. W. Whitelaw, and other hospital pathologists. Dr. C. O. Carter, Dr. F. N. Elcock, and Dr. C. Papp provided hospital records of affected relatives.

We are particularly indebted to Miss M. S. Gradwell, who recorded family histories in the homes of patients.

REFERENCES

- Abbott, M. E. (1927). *Nelson's Loose-Leaf Living Medicine*, 4, 207.
Campbell, M. (1949). *Quart. J. Med.*, 18, 379.
Cockayne, E. A. (1938). *Quart. J. Med.*, 7, 479.
Courter, S. R., Felson, B., and McGuire, J. (1948). *Amer. J. med. Sc.*, 216, 501.
Dogramaci, I., and Green, H. (1947). *J. Pediat.*, 30, 295.
Lamy, M., and Schweiguth, O. (1950). *Ann. Pædiat.*, 174, 65.
MacMahon, B., McKeown, T., and Record, R. G. (1953). *Brit. Heart J.*, 15, 121.