A Family Study of Atrial Septal Defect

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Family studies, largely based on questionnaires, of patients suffering from atrial septal defect have shown a small but significant increase in the number of close relatives affected by congenital heart malformation (Campbell and Polani, 1961; Lamy, de Grouchy, and Schweisguth, 1957). A more recent family study, where available parents and sibs of affected patients were interviewed and clinically examined, revealed a higher proportion of affected relatives (Nora, McNamara, and Fraser, 1967b). A further series seemed worth while, particularly one giving information on the occurrence of cardiac malformation in offspring of patients with atrial septal defect. The results of such a study are reported here.

Method and Material

Records of the Wessex Cardiothoracic Centre were searched and an attempt was made to trace those patients who had attended the Centre during the period January 1960-1966, in whom the diagnosis of atrial septal defect was made by clinical methods and electrocardiographic findings, and confirmed by cardiac catheterization, surgery, or necropsy. Those living far overseas were excluded, as were those patients who had died and whose parents were not available for interview. A particular effort was made to trace adult patients in order to gain information about their offspring. To obtain a homogeneous group, patients were excluded if a final diagnosis of ostium primum defect was reached, or if the atrial septal defect formed only a minor component of a more complex lesion.

Eventually 136 patients were invited to participate in the study. One did not wish to co-operate, so 135 patients from 131 families were included as index patients. These patients and their families were visited and a full social and family history elicited. Wherever possible, parents, sibs, and offspring were examined. No relative was included as suffering from congenital heart malformation unless there was confirmatory evidence from hospital records or death certificate.

The index patients were grouped according to the cardiological diagnosis (Table I).

TABLE I
CARDIAC MALFORMATION IN INDEX PATIENTS

	Total	Male	Female
Group I: ostium secundum defect only	99	30	69
Group II: ostium secundum defect with other cardiovascular anomaly	25	10	15
Group III: sinus venosus type defect	11	7	4
Total index patients	135	47	88

Group I comprised 99 patients (30 male and 69 female) in whom an ostium secundum defect was the only cardiovascular malformation.

Group II comprised 25 patients (10 males and 15 female) in whom an ostium secundum defect was associated with some other cardiovascular abnormality. Anomalous venous drainage, pulmonary valve stenosis, and ventricular septal defect were the most common associated anomalies, but aortic coarctation, persistent ductus arteriosus, mitral stenosis, and subaortic stenosis were also found.

Group III comprised 11 patients (7 male and 4 female) in whom a sinus venosus type defect was diagnosed. These were all associated with some degree of anomalous venous drainage.

A female preponderance was found among the index patients, giving a sex ratio of 0.53. This preponderance was most marked among the patients with isolated secundum defects.

Associated Non-cardiac Malformations in Index Patients. One index patient had Down's syndrome and two were educationally subnormal. Three children had strabismus, one had accessory nipples, and one accessory auricles. One child had had an operation for pyloric stenosis. Minor skeletal abnormalities included two bifid ribs in a boy, and triphalangeal, finger-like thumbs in a girl, similar to those described by Holt and Oram (1960) associated with atrial septal defect. Neither the parents nor the sibs of this index patient had a similar thumb or cardiac abnormality.

Twins. Four of the index patients were one of twins; in no case was the co-twin affected. One pair was of unlike sex and one female pair was known to be dizygotic. In the other two female pairs there was insufficient evidence to determine zygosity.

Results

Summaries of the families are given in Appen-
dixes A, B, and C.

(1) **78 Index Patients whose Mothers were Interviewed.** These index patients were distributed as follows. Group I: 53 patients (20 male and 33 female); Group II: 19 patients (10 male and 9 female); Group III: 6 patients (5 male and 1 female).

Maternal and Environmental Factors. The distribution of index patients by *maternal age and birth order* (Tables II and III) was compared with the Registrar General's figures for the relevant year of birth. (The index patient with Down's syndrome was excluded because of the known association between this syndrome and high maternal age.) The results showed no significant variation from the expected distribution.

The *social class* of each index patient was determined by the father's employment according to the Registrar General's classification of occupation (1960). A high proportion of parents in the armed services was noted, due probably to the presence of large naval and military bases within the region,

but no other significant variation from the distribution in the general population was noted (Table IV).

The *season of birth* of each index patient was tabulated (Table V). The results showed no variation from the expected distribution.

Maternal health during the relevant pregnancy: during the first trimester of pregnancy two mothers had rubella and one had measles. Vaginal bleeding was reported by two mothers during early pregnancy (2.6%). This is similar to the finding of Turnbull and Walker (1956) of 2-4% threatened abortion in all pregnancies. One mother admitted trying to procure an abortion with purgatives.

Sibs of These 78 Index Patients. Stillbirths, abortions, normal, and affected sibs occurring within the family (excluding the index patient) are tabulated in Table VI. The figures have been scrutinized, and no significant differences are revealed in the results of the pregnancies before the index patient and those after the index patient; nor were there differences between the families where the index patient was male and the families where the index patient was female. Thus the total figures are considered. The 212 pregnancies resulted in 22 abortions (10.3%). This figure does not differ significantly

TABLE II
MATERNAL AGE AT BIRTH OF INDEX PATIENTS

Maternal Age (yr.)	< 20	20-24	25-29	30-34	35-39	40 +	Total	
Group I	1 2.8837	20 15.1583	9 16.2804	15 10.4733	6 5.5153	1 1.6890	Observed	52
Group II	2 1.2736	2 5.7263	6 6.0266	5 3.6450	2 1.7846	2 0.5439	Observed	19
Group III	0 0.3457	1 1.7534	2 1.9273	1 1.1373	1 0.6399	1 0.1964	Observed	6
Total	3 4.5030	23 22.6380	17 24.2343	21 15.2556	9 7.9398	4 2.4293	Observed	77
							Expected	77

$\chi^2 = 5.9717.$

TABLE III
PARITY OF MOTHERS AT BIRTH OF INDEX PATIENTS

	Previous Live Births						Total	
	0	1	2	3	4	5 +		
Group I	19 20.826	13 15.559	9 7.790	5 3.681	1 1.842	5 2.302	Observed	52
Group II	7 7.403	8 5.651	3 2.957	1 1.433	0 0.715	0 0.841	Observed	19
Group III	3 2.379	2 1.845	0 0.901	0 0.414	0 0.205	1 0.256	Observed	6
Total	29 30.608	23 23.055	12 11.648	6 5.528	1 2.762	6 3.399	Observed	77
							Expected	77

$\chi^2 = 3.390.$

TABLE IV
SOCIAL CLASS OF INDEX PATIENTS

	Social Class					Armed Forces
	I	II	III	IV	V	
Group I	2	12	22	10	1	6
Group II	0	5	5	5	3	3
Group III	0	0	5	0	1	1
Total	2	17	32	15	2	10
General population (Southampton)	1.98	10.21	37.72	7.55	10.54	

TABLE V
SEASON OF BIRTH OF INDEX PATIENTS

	Jan.-Mar.	Apr.-June	July-Sept.	Oct.-Dec.
Group I	9	19	11	14
Group II	5	4	3	6
Group III	0	0	2	4
Total	14	23	16	24

from the 15% estimated as the expected abortion rate among all pregnancies by Warburton and Fraser (1964). Seven stillbirths resulted from the 190 pregnancies that proceeded beyond 28 weeks' gestation; two of these were due to non-cardiac malformation (one anencephalic and one meningo-myelocoele), two were due to toxæmia in the mother, two were due to obstetric trauma, and in one case the cause was unknown.

Besides the two stillbirths due to major malformation of the central nervous system, one sib had a severe scoliosis, one had a cleft palate, and one had Down's syndrome. Five instances of major mal-

formations among 190 sibs (2.6%) is similar to the random expectation of about 2.5% of all births (McKeown and Record, 1960).

There were 12 sibs (5 male and 7 female) found to have a *congenital cardiac lesion* among the 190 (6.3%). Four families each had two affected children. In two of these families the lesion was identical; two sisters had an ostium secundum defect and a small ventricular septal defect (No. 71 and 72), and a brother and sister had ostium secundum defects (No. 16 and 45). In a third family the lesions were similar, a girl with an isolated secundum defect and her brother with a similar septal defect and an associated aortic coarctation (No. 34 and 60). In the fourth family, the index patient (No. 47) had an isolated ostium secundum defect and her brother had a ventricular septal defect. In a further family there were six affected children. The index patient (No. 17) had an ostium secundum defect, one brother and one sister had atrial and ventricular septal defects, one brother had a ventricular septal defect with mitral stenosis, and a further brother had a ventricular septal defect with coarctation of the aorta. A fourth brother had left ventricular cardiomyopathy.

Among the 17 half-sibs of index patients, one was affected with a cardiac malformation. The male index patient (No. 54) with a secundum defect and subaortic stenosis had a paternal half-brother with subaortic stenosis.

(2) Findings in Series as a Whole.

Sibs of Remaining Index Patients. The other 57 index patients (12 male and 45 female) were

TABLE VI
RESULTS OF PREGNANCIES IN MOTHERS OF INDEX PATIENTS

Sex of Index Patient		Stillborn	Abortion	Unaffected Sibs		Affected Sibs	
				Male	Female	Male	Female
<i>Group I</i>							
M F	Born before index patient	1	6	24	17	4	2
	Born after index patient	0	1	10	5	0	0
	Born before index patient	1	4	21	16	0	0
	Born after index patient	0	4	15	23	3	0
<i>Group II</i>							
M F	Born before index patient	3	2	2	6	0	1
	Born after index patient	0	0	4	5	0	0
	Born before index patient	1	3	0	3	0	1
	Born after index patient	0	2	6	2	0	1
<i>Group III</i>							
M and F	Born before and after index patient	1	0	8	4	0	0
	Total pregnancies: 212	7	22	90	81	7	5
<i>Half-sibs</i>							
	Born before index patient	0	0	4	4	1	0
	Born after index patient	1	0	4	3	0	0
	Total pregnancies: 17	1	0	8	7	1	0

questioned about their sibs. Close family information was incomplete, but 4 sibs with proven congenital heart malformations were found among 204 known sibs (1.9%).

Parental Consanguinity. The parents of index patient No. 127 were first cousins, and those of index patient No. 49 were second cousins. None of the five sisters in the sibships was affected with congenital heart malformation, nor was the one brother.

Offspring of Index Patients. Among the adult index patients, 35 females and 10 males had offspring. They were distributed as follows. Group I: 8 males and 27 females; Group II: 5 females; Group III: 2 males and 3 females.

The results of the pregnancies are tabulated in Table VII. There was a total of 121 pregnancies resulting in 110 live births, 1 stillbirth, and 10 abortions (8.5%). Three of these children had non-cardiac congenital malformations, i.e. hydrocephalus, fragilitas ossium, and a giant naevus (2.7%). These figures show no significant increase over the expected incidence of stillbirth, abortion, and congenital non-cardiac malformation in the general population.

Congenital cardiac lesions were found in 10 of the 111 offspring (9%). These 10 affected children (6 male and 4 female) were all among the 82 born to affected mothers, none of the 29 children born to affected fathers being themselves affected. Two mothers with isolated secundum defects (No. 87 and 88) each had an affected daughter, one with an identical lesion to herself and the other with a ventricular septal defect. A mother with a secundum defect and anomalous venous drainage (No. 117) bore a daughter who at necropsy was found to have mitral stenosis, aortic coarctation, and a persistent ductus arteriosus. A mother with a sinus venosus type defect (No. 121) bore a son with a ventricular septal defect, and one mother with an isolated secundum defect (No. 89) bore 5 affected boys and one affected daughter. One of her sons (No. 17) had an identical lesion to hers, and the lesions

found in her other offspring have been described earlier in the results section.

Congenital Heart Malformation in Further Relatives. One father and one mother of index patients with ostium secundum defects had identical lesions to their children (No. 15 and 17). One other mother and two fathers had suggestive histories and clinical signs but had not been fully investigated. Among 29 grandchildren, 2 were known to be affected, and in 1063 first cousins one was found to have an ostium secundum defect and another died of congenital heart disease thought to be a septal defect. Among 322 nephews and nieces, one had an ostium secundum defect and another a more complex lesion.

Cardiological Diagnosis in Affected First Degree Relatives. The cardiac lesions found in the 26 affected first degree relatives of index patients are tabulated in Table VIII. In 8 cases the lesion found in the relative was identical to that in the index patient, and in a further 6 relatives it was partially so, an atrial septal defect being found in all these 14 relatives. Among the remaining relatives, 7 had ventricular septal defects, 4 in one family showed left ventricular cardiomyopathy, and 1 had mitral stenosis and aortic coarctation with a patent ductus arteriosus.

Discussion

Familial aggregation of atrial septal defect is apparent in the results of this family study. A recurrence of congenital heart malformation in 6.3% of sibs of index patients is a higher rate than was reported by Campbell and Polani (1961) or by Nora *et al.* (1967b). The recurrence in 9% of offspring of index patients in this study, and the high rate of recurrence in sibs is partly due to the inclusion of a remarkable family where both mother and son were index patients and there were six affected children (Fig.). In this particular family, left ventricular cardiomyopathy occurred in the father (I.1) and

TABLE VII
OFFSPRING OF INDEX PATIENTS

Sex of Index Patient		Stillborn	Abortion	Unaffected Offspring		Affected Offspring	
				Male	Female	Male	Female
M	Group I	0	0	14	10	0	0
F	Group I	0	3	32	22	5	3
F	Group II	0	5	4	5	0	1
M	Group III	0	0	4	1	0	0
F	Group III	1	2	6	2	1	0
	Total pregnancies: 121	1	10	60	40	6	4

TABLE VIII
CARDIAC MALFORMATION IN FIRST DEGREE RELATIVES OF INDEX PATIENTS

Sex and Index No.	Identical Malformation	Malformation Including Atrial Septal Defect	Malformation Including Ventricular Septal Defect	Other Malformation
Group I				
F 45	Brother, index patient 16 Sister, index patient 45	Brother, index patient 60, ASD and coarctation of aorta	Brother, VSD	Brother, LVC; son, LVC; father, LVC Brother, LVC
M 16				
F 34				
F 47	Father Daughter	Son, ASD and VSD; daughter, ASD and VSD	Daughter, VSD Son, VSD and MS; son VSD and coarct.	
M 15				
F 87				
F 88	Son, index patient 17	Brother, ASD and VSD; sister, ASD and VSD	Brother, VSD and MS; brother, VSD and coarct.	
F 89				
M 17	Mother, index patient 89			
Group II				
F 71 (ASD and VSD)	Sister, index patient 72	Sister, index patient 34, ASD		Daughter, MS, PDA, and coarct.
F 72 ASD and VSD	Sister, index patient 71			
M 60 (ASD and coarct.)				
F 117 (ASD and AVD)				
Group III				
F 121			Son, VSD	

Abbreviations: ASD—atrial septal defect; VSD—ventricular septal defect; MS—mitral stenosis; PDA—patent ductus arteriosus; coarct.—coarctation of aorta; AVD—anomalous venous drainage; LVC—left ventricular cardiomyopathy.

brother (II.2) of the index patient and in one of her sons (III.3). McKusick (1964) has described this condition as a single gene affect transmitted as a dominant trait, and this pedigree is consistent with a dominant mode of transmission with reduced penetrance, as there is no evidence of cardiomyopathy in the index patient (II.1). The occurrence of a second, probably unrelated, congenital cardiac disease in this family, and the fact that this one family has contributed so much to the high rates of recurrence in first degree relatives found in this series, make it seem wise not to include this family

for the purpose of calculating the recurrence rates. Excluding this family, recurrence of congenital heart malformation was found in 3.7% of sibs of index patients (a figure close to the 3.6% reported by Nora *et al.*, 1967b) and in 3.8% of offspring of index patients.

Studies of the maternal age and parity at the birth of the index patient and the social class of the family gave no evidence of these environmental factors being involved in the aetiology of atrial septal defect. Landtmann (1965) found an increase in the number of babies born with atrial septal defects in late summer and early autumn, corresponding he suggests with the winter occurrence of acute viral infections, which would affect the mother in early pregnancy. This finding is not confirmed in the present series where no significant trend in the season of birth of the index patients was noted.

The twins in this study showed no concordance for atrial septal defect. Uchida and Rowe (1957) reported no increased concordance for congenital heart malformation among monozygotic twin pairs than among dizygotic pairs. A personal study by Nora *et al.* (1967a) reported two monozygotic twin pairs where both twins were affected with atrial septal defect, and three dizygotic twin pairs where only one twin was affected with atrial septal defect. Though these figures are small, they support the suggestion that genetic factors are involved in the aetiology of atrial septal defect.

FIG. Pedigree of index patients 17 and 89.

Some families in the present series (No. 15, 87, 88) suggest a dominant mode of transmission, whereas others (No. 16, 45, 71, 72) suggest a recessive mode. However, the over-all recurrence rate does not support any simple Mendelian pattern. It has been shown that polygenic inheritance can mimic a Mendelian pattern (Edwards, 1960), and it is suggested that the results of the present study can be explained on the hypothesis that the genetic predisposition to atrial septal defect is polygenic.

Similarity of the lesion in affected relatives of patients with atrial septal defect has been noticed in previous reports (Christensen and Nelson, 1963; Carleton, Abelman, and Hancock, 1958). In the present series, 4 of the 26 affected first degree relatives suffered from left ventricular cardiomyopathy and came from the one family. In the remaining 22 first degree relatives, only 8 showed an identical lesion to the index patient, but 14 (63.6%) had an atrial septal defect. Thus, 63.6% of the 3.7% of first degree relatives found to have a congenital cardiac malformation had an atrial septal defect—a recurrence of atrial septal defect in 2.35% of first degree relatives.

The incidence of congenital heart malformation has been estimated to be about 6 per 1000 births, and in a Liverpool series Hay (1966) found a defect of the atrial septum in 11.7% of affected babies; the incidence of atrial septal defect, estimated from these figures, is 0.07% of births. Using the method described by Falconer (1965), with a population incidence of 0.07% and an incidence in first degree relatives of 2.35%, the heritability of atrial septal defect is about 70% ($69\% \pm 9\%$).

The sharp fall-off in the proportion of second degree relatives affected is in accordance with polygenic inheritance (Carter, 1961, 1969), and is in contrast to the expected even halving of the proportion affected with each degree of relationship, if a dominant gene with a reduced penetrance were involved. A deviation from the normal sex ratio with a preponderance of females was found, as in previous studies (Campbell and Polani, 1961). There is, however, no evidence from the families now reported, that the relatives of the less commonly affected sex are more at risk than those of the commonly affected sex, but the male deficit is not large enough for any considerable increase in risk to be expected.

With polygenic inheritance, the risk of the abnormality occurring within a family is increased if there are affected close relatives. The large family in the present series, in which a mother and five of her children have septal defects, and the families described by Nora *et al.* (1967b) and by Campbell and

Polani (1961) with many affected members, could represent families where many of the predisposing genes are concentrated.

Two consanguineous marriages among the parents of 135 index patients is possibly higher than expected in the general population, but is compatible with polygenic inheritance (Carter, David, and Laurence, 1968). None of the 6 sibs of the consanguineous sibship was affected with atrial septal defect, so there was no recessive subgroup detectable by parental consanguinity in this series. It has been suggested that recurrence of anomalies within a sibship is as likely to be due to persistence or recurrence of environmental factors as to a common genetic inheritance (Yen and MacMahon, 1968). The finding in the present series of recurrence of atrial septal defect as frequently in the offspring of index patients as in their sibs, together with Nora *et al.* (1967a) reporting a higher concordance in monozygotic twins than in dizygotic twins, indicate that genetic factors are of importance in the aetiology of atrial septal defect. The figures presented in this paper on the familial occurrence of atrial septal defect can be explained by polygenic inheritance.

Summary

Results of a family study of 135 index patients suffering from congenital atrial septal defect are reported.

Maternal age and parity, maternal health during pregnancy, season of birth, and social class studies gave no evidence of these environmental factors being involved in aetiology.

In all, 3.7% of sibs and 3.8% of offspring of index patients were affected with congenital heart malformation, the cardiac lesion being an atrial septal defect in 63% of affected first degree relatives. The heritability is estimated at 70%. These findings are compatible with the hypothesis that the predisposition to atrial septal defect is polygenic.

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APPENDIX A

Index Patients Whose Mothers Were Interviewed

Abbreviations: sb, stillborn; *, relative affected with congenital heart defect; ASD, atrial septal defect; VSD, ventricular septal defect; MS, mitral stenosis; M. inc., mitral incompetence; PDA, persistent ductus arteriosus; PVS, pulmonary valve stenosis; AVD, anomalous venous drainage; IP, index patient.

Index No.	Month and Year of Birth	Maternal Age	Paternal Age	Male Sibs	Female Sibs	Half-sibs		Other Affected Relatives
						Male	Female	
Group I: Male Index Patients								
One-child family								
1	4.61	23	26					
Two-child families								
2	6.61	30	32	1963				
3	3.59	25	30	1964				
Three-child families								
4	9.47	31	35	1940, 1944				
5	8.52	25	25		1950, 1956			
6	4.57	27	28	1954	1960			
7	4.62	24	25	1960	1963			
8	10.41	23	25	1935, 1939		1962	1950 (sb), 1951, 1953	
9	11.59	22	24	1961	1957			
Four-child families								
10	7.48	34	45	1942, 1943, 1948		1934, 1938	1935	
11	6.59	31	35	1950	1952, 1956			
12	3.48	20	23	1950, 1957, 1965				
13	3.45	33	41	1936, 1940	1938			
14	12.38	21	28	1940	1946, 1948			
15	11.62	38	43	1944	1950, 1961(sb)			Father* ASD
16	8.57	25	27	1960	1954, 1956*(IP45)			
Six-child family								
17	6.62	24	30	1956*1958* 1959*1961*	1960*			Mother*(IP89)
Eight-child families								
18	2.53	39	39	1942, 1943, 1945, 1946, 1948, 1949, 1950				
19	10.55	34	36	1953, 1957, 1959	1945, 1947, 1949, 1951			
Ten-child family								
20	5.50	37	44	1940, 1941, 1946	1934, 1936, 1938, 1944, 1947, 1949			
Group I: Female Index Patients								
One-child families								
21	4.46	28	34					
22	2.45	30	42					
23	11.56	23	26					
24	4.57	23	25					
Two-child families								
25	1.47	26	27	1956				
26	11.47	26	25		1950			
27	2.58	37	44	1949				First cousin* ASD
28	11.59	22	27		1962			
29	12.60	33	33	1963				
30	11.43	23	25	1945		1956	1964	
31	10.49	30	50		1942			
32	8.47	32	33		1951			
33	8.55	25	26	1959			1950	
Three-child families								
34	3.57	23	28	1959*(IP60)	1965			
35	1.62	23	29		1960, 1965			
36	1.59	40	42	1960	1956			
37	12.56	33	36	1945, 1952				
38	8.44	35	35	1938	1940			
Four-child families								
39	9.56	25	18	1957, 1958	1960	1954		First cousin once removed*(IP50)
40	12.55	22	24	1954	1957, 1964			
41	3.54	32	34	1946	1949, 1951			
42	3.60	36	37	1949	1951, 1953			
43	7.55	22	32	1953, 1954	1952(sb)	1964		
44	6.53	33	43	1938, 1946	1937			
45	5.56	24	26	1957*(IP16), 1960	1954			
Six-child families								
46	11.51	33	39	1945, 1957	1938, 1939, 1942			
47	9.54	23	25	1957, 1960*(VSD)	1956, 1958, 1962			
48	12.49	21	23	1951, 1952	1949, 1953, 1955			

APPENDIX A—continued

Index No.	Month and Year of Birth	Maternal Age	Paternal Age	Male Sibs	Female Sibs	Half-sibs		Other Affected Relatives
						Male	Female	
<i>Seven-child family</i> 49	4.46	19	21	1957	1948, 1950, 1952, 1959, 1963			
<i>Eight-child families</i> 50	10.49	23	25	1953, 1960	1951, 1952, 1955, 1962, 1964			First cousin once removed* (IP 39)
51	9.57	44	46	1932, 1937, 1938, 1946, 1950, 1952	1954			
<i>Twins</i> 52	3.55	32	36	1945, 1955 (co-twin)	1946			
53	7.58	22	29	1954, 1956 <i>Group II: Male Index Patients†</i>	1958 (co-twin)			
<i>One-child family</i> 54 M. inc. Subaort. stenosis	2.56	42	?			1940, 1949* (subaortic stenosis)	1935, 1936	
<i>Two-child families</i> 55 PDA	9.63	31	31		1960			
56 VSD	8.60	27	33		1962			
57 DVS	2.59	27	27	1963				
<i>Three-child families</i> 58 AVD	1.65	19	23	1964	1966			
59 AVD	8.59	37	37		1943, 1946			
60 Aortic coarct.	11.59	25	40		1957* (IP34)			
<i>Four-child family</i> 61 VSD	6.60	19	24	1965	1959, 1962			
<i>Five-child family</i> 62 AVD	12.64	30	32	1957(sb), 1962	1960(sb), 1955(sb)			
<i>Six-child family</i> 63 PVS	12.55	30	31	1957, 1960 <i>Group II: Female Index Patients†</i>	1948, 1950, 1962			
<i>Two-child families</i> 64 PVS	11.33	40	41		1930			
65 VSD	3.62	22	26	1966				
66 AVD	9.56	31	30		1962			
67 PVS	10.33	38	39		1935			
<i>Three-child families</i> 68 PVS	2.61	26	32	1963	1959			
69 Aort. coarct.	8.52	22	25	1954, 1955				
70 PVS	10.63	31	40	1962(sb)	1956			
71 VSD	11.55	26	24	1958	1956* (IP72)			
72 VSD	12.56	27	25	1958 <i>Group III: Male Index Patients</i>	1955* (IP71)			
<i>One-child family</i> 73	9.63	25	26					
<i>Two-child families</i> 74	8.58	23	29		1962			First cousin once rem.*ASD; first cousin once rem.*VSD
75	9.48	34	37		1942			
<i>Four-child family</i> 76	4.57	35	32	1955, 1964	1961(sb)			
<i>Seven-child family</i> 77	7.49	40	42	1943, 1945, 1946, 1948 <i>Group III: Female Index Patient</i>	1935, 1936		1932	
<i>Three-child family</i> 78	6.48	26	30	1952, 1960				

† Associated cardiac lesion is indicated immediately after Index No.

APPENDIX B

Index Patients With Offspring

Abbreviations: sb, stillborn; *, relative affected with congenital heart defect; ASD, atrial septal defect; VSD, ventricular septal defect; MS, mitral stenosis; M. inc., mitral incompetence; PDA, persistent ductus arteriosus; PVS, pulmonary valve stenosis; AVD, anomalous venous drainage; IP, index patient.

Index No.	Month and Year of Birth	Male Sibs	Female Sibs	Male Offspring	Female Offspring	Other Affected Relatives
79	5.19	1925, 1930	<i>Group I: Male Index Patients</i>			
80	4.26	1921, 1923, 1933	1920	1951	1948	
81	7.09			1931, 1933, 1935, 1941	1949	
82	? 30	10 sibs		1952, 1958	1936, 1938	
83	8.35	5 brothers	5 sisters (1924*ASD)	1964	1950, 1954, 1963	Brother's son*ASD
84	9.46	1948		1954, 1958, 1962	1962, 1965	First cousin once rem.*(IP85)
85	10.22			1951, 1960	1957	First cousin once rem.*(IP84)
86	12.26	1922, 1924, 1931	<i>Group I: Female Index Patients</i>			
87	11.44	1941, 1947		1963	1965*ASD	
88	10.28	1921(sb)		1951, 1963	1961*VSD	
89	8.38	1945*LVC		1956,* 1958*, 1959,* 1961,* 1962*(IP17)	1960*	Father*; First cousin*
90	11.28	1930		1964	1963, 1949	
91	10.12	1917	1914		1939	
92	10.22		1915, 1918		1946, 1951	
93	11.31	1926, 1930, 1934	1936	1956, 1960		
94	3.14		1919, 1916	1945		
95	3.22	1926, 1928	1932	1943, 1950, 1955		
96	1.31	1947	1943, 1946	1952, 1955		
97	2.16	1914, 1918	1912	1950		
98	8.08	4 brothers	4 sisters (1920*)	1932, 1942, 1944	1927, 1937, 1940	
99	8.16	1917, 1921	Twins 1923	1941, 1943	1939, 1945	
100	7.37				1965	
101	3.37	1934, 1946, 1950, 1955	1940(sb), 1951, 1958		1963	
102	7.12	1 brother	7 sisters	1938	1936, 1943	Granddaughter*
103	5.39	1924, 1926, 1930, 1942	1935	1963		
104	5.34		1940	1964	1962	
105	6.16			1939		
106	4.43	1924, 1926, 1928, 1932, 1936	1922, 1927, 1929, 1930, 1934, 1941	1963		
107	1.13	5 brothers	4 sisters	1933, 1951	1937	
108	2.13	1914, 1916, 1918, 1919, 1920	1912, 1924, 1926	1936, 1938, 1940	1942	
109	3.29	1927, 1930, 1933, 1935, 1937, 1938, 1941		1954	1949, 1950	
110	2.48	1944, 1951	1949, 1956, 1960	1966		
111	2.32	1929, 1932(sb), 1934, 1953*		1959	1961	
112	9.11	5 brothers	1 sister		1937	Granddaughter*
113	1.36	1939, 1945	1935, 1937, 1942	1959	1958	Niece*
114	2.46		<i>Group II: Female Index Patients†</i>			
(AVD)			1944	1966	1965	
115	12.34	1930	1940	1960	1956	
(AVD)				1962		
116	8.30	1935		1957	1960, 1962*(MS, PDA, coarct.)	
(AVD)			2 sisters		1962	
117	2.30	3 brothers				
(AVD)						
67 (see Appendix A)						
Twin						
118	1.32	5 brothers	6 sisters, twin sister	1964	1958	
(MS)						
119	5.24	1930	<i>Group III: Male Index Patients</i>			
120	11.39	1945	1922	1949, 1954	1945	
			1943	1961, 1963		
121	3.21	1924, 1928	<i>Group III: Female Index Patients</i>			
				1946*(VSD), 1947, 1949, 1955		
122	5.27	1933		1951(sb), 1960, 1962	1956	
123	4.23	1915, 1919		1944		

† Associated cardiac lesion is indicated immediately after index No.

APPENDIX C
Index Patients Without Offspring Whose Parents
Were Not Available for Interview

Index No.	Month and Year of Birth	Sibs	
		Male	Female
Group I: Male Index Patients			
One-child family			
124	2.46		
Three-child family			
125	2.24	1926	1931
Group I: Female Index Patients			
One-child families			
126	4.24		
127	12:09		
Two-child families			
128	10.31		1934
129	4.07		1906
Three-child family			
130	2.40	1948	1942
Five-or-more-child families			
131	7.11	1908, 1916, 1927	1910
132	10.07	1891, 1900, 1911	1899, 1901
133	5.95	1885, 1888, 1894, 1897, 1899, 1901	1890, 1896
Twin			
134	9.38	1932	1934, 1938 (co-twin)
Group II: Female Index Patient			
135	11.20	3 brothers	3 sisters