FACTORS IN THE ÆTIOLOGY OF ATRIAL SEPTAL DEFECT

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The relative importance of heredity and environment in causing malformation of the heart is still uncertain. We hoped that details about the families of our patients might provide some evidence to help in this problem. After a preliminary enquiry about the families of 384 patients, most of whom had Fallot's tetralogy (Polani and Campbell, 1955), we thought it would be more useful to make our enquiries in more homogeneous groups. So far, we have covered 261 patients with persistent ductus arteriosus (Polani and Campbell, 1960) and 151 patients with coarctation of the aorta (Campbell and Polani, 1961).

In this paper we are applying the same method to the families of 170 patients with atrial septal defect. We are grateful to Dr. Evan Bedford for sending out our questionnaires to about 100 consecutive patients he had seen at the Middlesex Hospital: the 94 of these who replied (Cases 1-94) and 76 of our own patients (101-176) make up this series. We think that the diagnosis is certain in practically all these, and that the defect was of the ostium secundum type in all but three. In those seen at the Middlesex, it was confirmed by cardiac catheterization or operation in all, and generally by both. In the Guy's patients it was confirmed by catheterization, necropsy, or operation in all but five, in whom there seemed no doubt about the clinical diagnosis. Several had some pulmonary hypertension, but with A.S.D. this is generally a secondary result of the defect: in seven it was severe enough to have lessened the left-to-right shunt and produced a right-to-left shunt as well.

I. OTHER MALFORMATIONS IN THE PROPOSITI

(a) *Cardiac Malformations.* It is difficult to decide the frequency of these, because an atrial septal defect may often be a part of the picture in some more complex lesion, e.g. in tricuspid atresia or isolated lœvocardia, and may be hard to diagnose when combined with others, e.g. with Fallot's tetralogy. Such cases were excluded and this series was composed of examples of atrial septal defect (A.S.D.), relatively uncomplicated, though several were found to have some less important cardiac malformations as well.

Most were of the common ostium secundum type but two were of the ostium primum type (Cases 115 and 132) and a third was thought to be (150), so that probably all these three had a ventricular septal defect and some deformity of the A-V valves as well as an A.S.D. (1·8%). One of these (132) and one other (171) had a persistent left superior vena cava. Patients with *total* anomalous pulmonary venous drainage were excluded, but some degree of this is common with atrial septal defects, especially with the sinus venosus type. Five of our patients (2·9%) (Cases 20, 34, 118, 120, and 165) were thought to have some anomalous pulmonary venous drainage.

The combination of mitral stenosis with A.S.D. is well recognized: it occurred in eight of our patients (4·7%). Six of the Guy's patients (171-176) and three of the Middlesex ones (27, 31, and 87) had pulmonary valve stenosis also, an incidence of 5·3 per cent. Six others had systolic gradients across the pulmonary valve between 16 and 34 mm. Hg but, with the increased flows, these gradients

can not be taken as indicating organic pulmonary stenosis. In addition to these malformations, one patient had congenital aortic stenosis (156) and one had situs inversus (157): a third who had aneurysmal dilation of the *right* atrium was not counted, as this was probably a secondary effect of her A.S.D. Combining all these groups, there were 15.9 per cent with some additional malformation.

(b) *Non-cardiac Malformations.* This section is limited to the 76 patients from Guy's Hospital, as no specific question was included in the questionnaire. Many of them had deformed chests, but as these were generally secondary to the large heart that often develops at an early age, they have not been included as independent malformations. Most patients were thin with a narrow chest and long narrow hands and fingers and feet and often with a high arched palate, but we have included only one, a girl, as true arachnodactyly (130). We do not accept the view that there is a close association between A.S.D. and arachnodactyly, though the general appearance of the patients is often similar.

We have only two other examples with recorded malformations—a girl with bilateral cervical ribs (113) and a boy with an absent rib, a hemi-vertebra, and a speech defect (156). In addition, one Middlesex patient volunteered the information that she had had an operation for congenital pyloric stenosis (53).

Even three instances among 76 patients (4%) is more than would be expected by chance. Considering that in general the physique and development of these patients were less good than in most other groups with acyanotic congenital heart disease, we were surprised at the known incidence of other malformations being lower than we have found in persistent ductus, pulmonary stenosis, and coarctation of the aorta, where it was between 6 and 8 per cent for major malformations. Even so, we think our figures are lower than the true incidence, because we did not see many infants and were specially interested in patients where there was some chance of surgical treatment. Lamy *et al.* (1957) found other malformations in nearly 18 per cent of their patients with congenital heart disease, the highest proportion being in those with atrial septal defect (27%) and the lowest in those with coarctation (7%).

II. MALFORMATIONS IN SIBS OF PROPOSITI

(a) *Cardiac Malformations* (Table I). (1) Two sisters each had an atrial septal defect and in each the diagnosis was confirmed by catheterization and successful operation (21).

(2) Two other sisters each had an atrial septal defect, again confirmed by catheterization and successful operation, and a cousin also had a heart murmur but the cause was uncertain (90).

(3) A brother of one propositus had died at 9 days with congenital heart disease (129).

(4) An elder brother of another had been rejected for army service for "a slow heart rate and congenital enlargement of the heart" (155).

In addition to these four cases among the 378 sibs (1.1%) two with proved A.S.D., there were some more doubtful ones—two sisters of two patients were suspected to have A.S.D. (4 and 62); a mother and step-brother (with the same mother) had some heart disease, possibly A.S.D. (74); and a brother of another died when three days old, probably from heart disease (1). We can not be sure that any of these had an atrial septal defect but we should be surprised if some of them had not. Lamy *et al.* (1957) found that 2 sibs of their 97 propiti had congenital heart disease, one an atrial septal defect and the other Fallot's tetralogy. The incidence in our cases (1.1%) is less than we found for persistent ductus (2.1%) and simple pulmonary stenosis (2.2%), but more than we found for coarctation of the aorta (0.4%). In all groups the malformations were generally the same in the sibs as in the propiti.

(b) *Non-cardiac Malformations.* (1) The brother of one propositus had congenital pyloric stenosis (32).

(2) A brother died with leukæmia at the age of 14 years (82).

(3) A sister developed diabetes at 12 years (83).

(4) A brother had epilepsy and a large heart (91).

TABLE I
CARDIAC MALFORMATIONS IN SIBS, PARENTS, AND CHILDREN OF 170 PROPOSITI WITH ATRIAL SEPTAL DEFECT

Propositus		Additional case		
Case No. and method of diagnosis	Sex and age (1958)	Relation and age (1958)	Defect and method of diagnosis	Comments
21 C. Op. 90 C. Op. 129 C.	F. 24 F. 22 F. 8	Sister, 22 Sister, 13 Brother† died, aet. 9 days with C.H.D.	A.S.D. C. Op. A.S.D. C. Op.	
19 C. Op. 85 C. Op. 126 C. Op. 143 C. Op.	M. 14 F. 19 M. 19 M. 19	Mother, 35* Father† Mother, 52 Mother, 48	A.S.D. Cl. A.S.D. Cl. A.S.D. C. A.S.D. Cl.	Father died, aet. 52
121 C. Op. 170 Cl.	F. 28 F. 30	Son† died with C.H.D. after 13 hours Son, aet. 5 months (1960), has septal defect or P.D.A.		

C=diagnosis established by catheterization, Op. by operation, and Cl. on clinical grounds.

C.H.D.=congenital heart disease.

* An aunt and cousin were proved to have A.S.D. and probably several other relatives (see Fig. 1).

† Died.

- (5) A brother had congenital dislocation of the hip and died when two years old (133).
- (6) A younger sister was a mongol (151).
- (7) A younger sister had a deformed foot (156).
- (8) A sister had some abnormality of the bones and teeth (88).

Eight examples among 378 sibs (2.1%) is similar to the incidence of non-cardiac malformations that we found for the sibs of propositi with persistent ductus (2%), coarctation of the aorta (2.8%), and simple pulmonary stenosis (1.6%). This is probably no more than what might be expected by chance. Lamy *et al.* (1957) found the incidence only 1 per cent which was the same as in their controls.

III. MALFORMATIONS IN PARENTS AND CHILDREN OF PROPOSITI

(a) *Cardiac Malformations in Parents* (Table I). (1) The mother of the propositus also had A.S.D., and so had a first cousin and an aunt (Family 19: see p.482 and Fig. 1).

(2) The father of another had an A.S.D. (85).

(3) A mother and her son both had A.S.D. When the son was due to be admitted to hospital we were told his mother was ill with heart failure from mitral stenosis: we suggested that she might, in fact, have an atrial septal defect and this was confirmed by catheterization (126).

(4) The mother of another boy had been under observation for several years with A.S.D.: they have been fully reported (Campbell, 1959, Family 33) (143).

(5) A woman, aged 40, had been under observation for 12 years with A.S.D. Her mother had always been breathless and liable to faint, and died with congestive heart failure when she was 27 and her only daughter was three years old. Of the mother's seven sibs a sister died when she was 21 with long-standing heart disease, a brother died when he was 45 with congestive heart failure, and a sister developed cardiac symptoms when she was 50 years of age. There was no known rheumatic history in the family so it seems probable that some of these were examples of A.S.D. (159).

(6 and 7) The father and the mother of two propositi had systolic murmurs that were thought to be organic without any obvious cause, so that A.S.D. was possible or even likely (9 and 47).

Even omitting the last three families, 4 of the 318 parents with A.S.D. (1.3%) is unlike what we have found among the parents of our propositi with persistent ductus, coarctation of the aorta,

and simple pulmonary stenosis, where there were only 2 examples of congenital heart disease among 710 parents. Neither of these were concordant, the mother of a girl with a ductus having slight pulmonary stenosis, and the mother of a girl with coarctation having a persistent ductus: it is true that the father of another patient with coarctation had a history that was suspicious of coarctation but there was no proof. The significance of this frequency of A.S.D. in child and parent will be discussed later.

(b) *Non-cardiac Malformations in Parents.* There was nothing remarkable about these. The mother of one patient died when 40 from a ruptured cerebral aneurysm, having recovered from a similar attack six years before (40). The father of another and the patient herself both had curvature of the spine and a protruding left shoulder but we do not know if there was a hemi-vertebra (50). The mother of a third had had a successful operation for hare lip and cleft palate (176).

Three known non-cardiac malformations among 318 parents (1%) can not be taken as out of the ordinary, though it is a little more than the 4 examples we found among the 710 parents in the other groups. Lamy *et al.* (1957) found no instance of congenital heart disease and only 10 instances of other malformations among 2376 parents of their propositi (0.5%).

(c) *Malformations in Children.* We have little information about the children of our patients with A.S.D. Most of them were children and even for those who were married our information is incomplete. Among the 170 propositi we know about the families of 19: there were 23 children, 20 of whom were normal. Of the other three, one was spastic (20), one died with a congenital heart lesion after 13 hours (121), and the third, a son aged 5 months, born since this was first written, has signs suggesting a septal defect, probably an atrial septal defect (170). The numbers are too small to be significant, but as with the other groups of congenital heart disease, we have found enough to suggest they are more common than would be expected and that more data should be collected to prove or disprove this.

IV. MALFORMATIONS IN OTHER RELATIVES

- (a) *Cardiac Malformations.* (1) A first cousin had a successful operation for A.S.D. (19).
- (2) Another first cousin had a successful operation for A.S.D. (60).
- (3) A first cousin died with some form of congenital heart disease when 10 weeks old (26).
- (4) A first cousin was stillborn and was said to have congenital heart disease (118).
- (5) A first cousin had had a successful valvotomy for Fallot's tetralogy (125).
- (6) A boy, aged 8 had an ostium primum, and his second cousin had had a successful operation for a large V.S.D. (150).
- (7) A brother's son has a heart defect and had already had heart failure twice in the first year of life (85).
- (8) A cousin of the father had had an operation on his heart but its nature is not known (27).
- (9) The mother's father, two uncles, and two aunts all died suddenly from heart disease, some before they were twenty (83).
- (10) The grandmother's brother and sister both died with heart disease, aged 19 and 20 respectively (28).

Omitting the last three because we are not certain of the nature of the heart defect, there were seven examples of congenital heart disease among fairly close relatives, mostly first cousins. We can not say whether this is significant because we do not know the numbers at risk. There is, however, a larger number of heart defects among cousins than we have found for persistent ductus or coarctation, and two examples of proved A.S.D., three of some congenital heart disease, one of V.S.D., and one of Fallot's tetralogy again suggests that concordance of the lesions is more common than discordance, though not so constant as among sibs and parents.

(b) *Non-cardiac Malformations.* A first cousin (maternal) was born blind and with some paralysis, and died at 4 months; a first cousin (paternal) was born deaf and dumb with some degree of spasticity; and a child of a first cousin was born with spastic quadriplegia and was still alive after two years (52).

No other family has three examples of multiple defects, but an aunt of the father was a mongol (58), an aunt was mentally defective (60), a nephew had splenomegaly and ? cirrhosis (62), an uncle was born with "paralysis" but lived for 38 years (66), a sister's child had deformed fingers and toes (69), a twin sister's daughter had congenital dislocation of the hip (70), a nephew had a deformed hand and foot (115), and, of more doubtful significance, a grandfather had "hæmophilia of the gums" (14).

Considering the large but unknown number of relatives involved, it seems doubtful if these 11 examples are significant of any increased incidence, but the cases reported to us were certainly not complete. For example, we found out almost by chance that two cousins had both had operations for A.S.D. and this had not been mentioned by the propositi.

V. CONSANGUINITY OF PARENTS

An increased number of consanguineous marriages between the parents of propositi may reveal that the condition is inherited as a Mendelian recessive character. We have this information about the parents in 155 of our families and about the grandparents in all but one of these.

The parents were related in 6 instances. They were first cousins in 3 (50, 92, and the mother of 19), second cousins in 2 (11 and 31), and the father had married a daughter of his first cousin in the sixth (88). In Family 19, the propositus was born by an illegitimate union so that his mother's subsequent marriage to a first cousin (with two normal sons of the marriage) is not material: however, the mother herself had A.S.D. and was the child of a first-cousin marriage, so we have included her. The single patient with situs inversus was not the offspring of a consanguineous marriage.

In four other instances the grandparents were related, but we do not think these of any significance as the relationship was either on the paternal or maternal side and not between them. The father's parents were first cousins in two (127 and 147) and more remotely related in another (67), and the mother's parents were first cousins in the fourth (53).

Thus of the 155 cases, 3 were the offspring of first-cousin marriages (1.9 per cent) and 3 others of cousin marriages. This is more than four times as high as the incidence of first-cousin marriages among the general population (0.4%) and twice as high as we have found it among our other groups with congenital heart disease (0.9%). This was the experience of Lamy *et al.* (1957) also who found it highest in his groups of A.S.D. (3.9) and of pulmonary stenosis (4.4), where we have found it low, compared with 2.5 among all his cases of congenital heart disease and 0.7 among his controls. The high incidence in our series is due mainly to the Middlesex patients but we think this must be due to chance.

In any recessive condition the proportion of children derived from consanguineous marriages is related to the frequency of the recessive gene responsible and to the frequency of such marriages in the population from which the sample is drawn. It can be calculated approximately from the formula of Lenz (1919):

$$k = \frac{c}{c + 16q}$$

where *c* is the incidence of first cousin marriages in the population, i.e., 0.4 per cent for a hospital population in this country (Bell, 1940), and *q* is the square root of the frequency of the recessive trait.

The incidence of atrial septal defect and indeed of all congenital heart disease in the general population is uncertain. McMahon *et al.* (1953) found the latter 3.2 per thousand at birth, a little higher than earlier estimates, but Carlgren (1959) in Sweden found it 6.4 per thousand. Bonham-Carter (personal communication) finds this last estimate the most accurate and we have taken it to be 6 per thousand. Our own estimate of the frequency of atrial septal defect is 16 per cent of all congenital heart disease and Wood finds a very similar figure of 18 per cent, so we have assumed it to be 17 per cent, making the incidence of A.S.D. 1 (6 × 17/100) per thousand in the general population.

Assuming that A.S.D. were a recessive trait, its gene frequency would, therefore, be $\sqrt{0.001}$, i.e., 0.0316. The expected frequency of consanguineous marriages among parents of children with A.S.D. would be 0.78 per cent. The difference between this and the observed frequency of 1.9 for first cousin marriages does not quite reach the level of statistical significance. Nevertheless the observed frequency is so much higher than the expected frequency that we think a recessive gene is responsible for a proportion of the cases of atrial septal defect. It is interesting that this should be so when there is also evidence of dominant inheritance in other families with A.S.D. (see later). We are doubtful if both these mechanisms explain the occurrence of more than a proportion of all the cases of atrial septal defect.

Developmental disorders and mortality were very frequent in the children of consanguineous marriages among our families where the propositus had a persistent ductus. This was not so in the present series with atrial septal defect. In the six families where the parents were first or second cousins, there were 8 sibs of whom 7 were normal and 1 had some abnormality of the bones and teeth. In the four families where the grandparents were cousins, there were 12 normal sibs and one who died with pneumonia at the age of three months. In these ten families combined there were only three recorded miscarriages.

VI. FAMILIAL CASES OF ATRIAL SEPTAL DEFECT

In this section we shall discuss (1) families where atrial septal defect occurs in three or more generations, suggesting dominant Mendelian inheritance; (2) the concordance or discordance of the malformations in the members of a family; and (3) the relationship of the affected members.

Familial Incidence in Three or More Generations. It is uncommon to find examples of congenital heart disease in several generations but there are a few examples of this with atrial septal defect, though it may be difficult to establish the diagnosis in the earlier generations. We are, therefore, reporting our Family 19 more fully because there were four members with certain A.S.D. and four or perhaps five, others who were said to have "the family disease with a defective heart" in five generations (see Fig. 1).

FIG. 1.—Genealogical tree of Family 19 showing patients with atrial septal defect. ● patients proved to have A.S.D. ○ patients said to have "the family disease with a defective heart," ○ patients said to be without it. III 8 died suddenly at home: necropsy report, pulmonary embolism and heart disease.

The numbers *above* the line indicate the order of birth within each family, the position in this family tree being changed to show the two first-cousin marriages more easily.

The numbers *below* the patients symbols indicate the patients age in 1959, unless it is stated to be the age of death.

IV 8, the husband of IV 4 was our main informant about the family.

Cases V 7 and V 11 were both propoiti in this series: the former did not record that her cousin had heart disease, but fortunately the latter did: in both these the diagnosis was confirmed by catheterization and by successful closure of the atrial septal defect. When we first wrote this account Case IV 7 was included as one "who had the family disease"; but further enquiries revealed that she had been in Guy's Hospital under Dr. Charles Baker, who had had no doubt about the diagnosis of A.S.D.; and that the death certificate of Case III 8 was available.

Case IV 8 was our main informant about the family but IV 7 also had recorded it: we have checked with them the small points where they differed and think that Fig. 1 is correct. Case V 11 was illegitimate and as the mother lived in a small country town in the South of England and the father was a Canadian soldier, it is unlikely that they were related: subsequently, however, the mother of the propoitus married her first cousin and they have had two healthy sons. The mother, who also had clear clinical evidence of A.S.D., was herself the offspring of an earlier first-cousin marriage.

The evidence for an atrial septal defect in four members of the fourth and fifth generations has been given. Case V 1 died with congenital heart disease when 6 months old, so A.S.D. was possibly the cause. Case III 8, who was said to have the family disease, died suddenly: the death certificate attributed this to pulmonary embolism secondary to disease of the heart, so A.S.D. seems likely. We can adduce only the family tradition (proved to be correct for IV 7) as evidence for the three members of the first two generations. Only one of our informants included II 3 as having "the family disease", but as she died with dropsy when 50 (the same age of death as III 8) it seems probable that she should be included.

There are, therefore, 4 certain cases of A.S.D. and 5 probable cases (including V 1, not marked as such in Fig. 1) in five generations of this family. In five of these patients the descent was direct from mother to son, to his daughter, to her daughter, and finally to her son. This suggests dominant Mendelian inheritance, though in the other two the defect apparently skipped one generation. Nor is the ratio of affected to normal sibs (8:30) anywhere near the expected 1:1 ratio, so that if A.S.D. is sometimes inherited as a Mendelian dominant character, the degree of penetrance must be very incomplete.

Holt and Oram (1960) have reported a similar family where three sibs and the daughter of one of them had A.S.D. (one proved by necropsy) and five other members, including several of two earlier generations, were thought to have A.S.D. Three of those who were examined had similar deformities of the hands, especially the thumbs, and some members of the earlier generations were said to have had these also as well as the defect of the heart. They thought the inheritance was of the Mendelian dominant type.

Another family where a girl, her mother, and her grandmother all had an atrial septal defect, proved by necropsy in the last, has been reported (Campbell, 1949). Howitt (1961) has described a very similar family where a woman, her only daughter, and one of her two grandchildren, a girl, all had atrial septal defect: her parents and many of the collaterals were without any evidence of heart disease.

Zetterqvist (1961) found eight certain and five probable cases with A.S.D. of ostium secundum type in four generations of one family. We have not included them among the cases in our Table II because, in the short account of his communication to the Swedish Pediatric Society, the relationship of the subjects is not given. Chromosomal aberrations of varying type were found in some of these patients and an aberration in the form of a balanced translocation in a healthy member of the family.

It is difficult to avoid the conclusion that in some cases atrial septal defect is inherited as an autosomal Mendelian dominant character, and this is supported by the relatively large number where a parent and child were affected. The numbers in these four families are hardly enough for analysis but 19 of those affected were female and only 5 male: the condition was passed through men as well as through women. There is, therefore, no question of the condition being sex-linked.

Concordance or Discordance of Affected Pairs. Among our 157 families, there were 13 where two members and 1 where at least four members (Family 19) had congenital heart disease (C.H.D.), making 17 pairs in 14 families. These provide evidence about whether the malformations are the

same (concordant) or different (discordant) in the two members of the pair, while reported cases *may* have been reported just because the malformations were the same. In nearly all our cases of A.S.D. the diagnosis had been confirmed by cardiac catheterization or by operation or by both.

The cases reported by Lamy *et al.* (1957) should be equally reliable because they made enquiries about all malformations in their families. They reported 2 sibs of their 92 probands with A.S.D. as having congenital heart disease—one with A.S.D. and one with Fallot's tetralogy—and also 2 first cousins, again one with A.S.D. and one with Fallot's tetralogy.

Combining these, there were 21 pairs in 18 families. The malformation was the same in both members in 12 pairs and different in only 3 pairs. In the other 6 pairs, one had A.S.D. and the second had congenital heart disease but the type was not known, generally because the second had died in infancy. The figures for these 21 pairs are shown first in each column in Table II.

TABLE II
RELATIONSHIP OF PATIENTS AND NATURE OF DEFECTS WHERE THERE WERE TWO OR MORE IN A FAMILY

Relationship of pair	Number of pairs. First with A.S.D. in all.			Total
	Second with A.S.D.	Second with other known C.H.D.	Second with C.H.D. (type not known)	
Sibs	3+12	1+1 (1 coarct. and 1 Fallot)	1+1	5+14
Parent and child	4+13	0+1 (V.S.D.)	2+0	6+14
Cousins	4+0	2+2 (3 Fallot and 1 P.D.A.)	2+0	8+2
Uncle or aunt and nephew or niece	1+0	0+0	1+0	2+0
Total	12+25 37	3+4 7	6+1 7	21+30 51

C.H.D.=Congenital heart disease.

The first figure gives the numbers where all malformations in the family were recorded (present series, 17 pairs; and Lamy *et al.* (1957), 4 pairs). The second figure gives other collected or reported cases.

This table shows also (as the second figure in each column) the results in other pairs, some that we have collected and some that have been reported; and, in fact, the proportion with concordance was not much higher. In all, there were 37 pairs where both members of the pair had A.S.D. and only 7 where they had different malformations. The malformations in these seven pairs were A.S.D. in the probands, and in the other member Fallot's tetralogy (4), coarctation (1), ventricular septal defect with pulmonary stenosis (1), and persistent ductus arteriosus (1): it seems probable that the high incidence of Fallot's tetralogy is due to chance and would not be repeated in a larger series. In the other 7 pairs, one had A.S.D. and the other had congenital heart disease, the type not being known: as might be expected not very many cases of this group have been reported. We have found that where there are two cardiac malformations in a family it is much more common for them to be of the same type with other forms of congenital heart disease, as well as with A.S.D.

The Relationship of the Pairs Affected. Two examples of congenital heart disease in a family are found more often in two sibs than in a parent and child. Brown (1939) supported this view and Taussig (1947) found only 15 of 48 reported cases in more than one generation. Reporting 40 such families that he had seen, Campbell (1959) found 26 examples of sibs and only 9 of parent and child, the others being less close relatives: on the rather scanty evidence then available, he wondered if atrial septal defect might not be an exception to this rule. With the larger number of examples now available, it seems that this is so, and that atrial septal defect (and probably congenital aortic stenosis) are more likely to occur in parent and child than are most other forms of congenital heart disease.

In the first 21 pairs, 17 in our families and the 4 reported by Lamy *et al.* (1957), 5 were sibs, 6 were parent and child, 8 were first cousins, and 2 were uncle or aunt and nephew or niece. In addition to these pairs we have notes of some others but are considering them with the reported cases, because they may have come to our notice only because they were concordant, though we do not think that this was so.

Our family where grandmother, mother, and daughter were all affected has been mentioned. Deuchar (personal communication) has given us notes of two brothers, both of whom had successful operations for A.S.D. Bedford has given us notes of two pairs who were not included in the general enquiry which was confined to consecutive unselected cases: (1) two brothers, both with A.S.D. and (2) a girl, aged 11, and her father, both with A.S.D.

Besterman (personal communication) has given us details of a family where the first child died with congenital heart disease and cyanosis, aged $2\frac{1}{2}$ years; the second was a normal girl, aged 20; the third, a boy aged 17, had severe pulmonary hypertension with a reversed shunt through an A.S.D.; and the fourth, a girl aged 12, had an A.S.D. with a pulmonary arterial pressure of 70/30 mm. and a resistance of 8.5 units: both parents were normal. He has since told us of another father and daughter, both of whom had successful operations for A.S.D.

Among reported cases, Courter *et al.* (1948) described Lutembacher's syndrome in two sisters, aged 21 and 26. Davidson (1958) reported A.S.D. in a mother and two (and probably a third) of her eight children: he had not been able to find many other reported examples but found two in a parent and child and two in sibs. Since then some other examples have been reported. Carlton *et al.* (1958) have described a sister with A.S.D. and a brother with coarctation; two sisters and a daughter of one of them, all with A.S.D.; and three sisters with A.S.D. and the daughter of one of them probably with ventricular septal defect and pulmonary stenosis. The families of Holt and Oram (1960), and of Howitt (1961) have already been mentioned. More recently Davidson (1960) had added two pairs of cousins, the second members having had operations for persistent ductus and Fallot's tetralogy respectively. He thought there were probably other close relatives with congenital heart disease in 7 of his 132 cases of A.S.D.

These results have been added to our figures in Table II: the total of 51 pairs was composed of sibs in 19 instances (15 concordant), of parent and child in 20 instances (17 concordant), of first cousins in 10 instances (4 concordant), and of uncle or aunt and nephew or niece in 2 instances (1 concordant). This is a much higher incidence of pairs of parent and child than we have found in most other forms of congenital heart disease, except in congenital aortic stenosis: generally the great majority of pairs are composed of sibs.

VII. THE INFLUENCE OF PARENTAL AGE AND BIRTH ORDER

The age of the parents was not obviously different from what might be expected. Some patients with A.S.D. were the first-born children of young mothers, some were later-born in the families, and some were the children of quite elderly parents. In the 157 mothers where the age was known, the mean age at the time the affected child was born was 28.86 years, and this is near the expected mean age of mothers at the birth of their children among the general population.

Penrose (1955) thinks that the difference between mean paternal and maternal ages is in some ways a more useful measurement, and that when the paternal age is increased unduly it suggests a genetic case, because the larger number of cell divisions in the male germ-line may encourage a "failure to copy genes correctly." We know the age of both parents in 150 pairs and the mean ages were 29.05 years for these mothers and 32.08 years for the fathers, calculated to the nearest month in each case. The difference between the paternal and maternal mean ages is 3.03 years and this is more than the difference of 2.3 years found in the general population of England and Wales. The difference was increased in our series of patients with persistent ductus (3.3 years) and coarctation of the aorta also (2.87 years).

It is hard to know how much, if any, significance can be attached to this difference. It is, of course, well-known that when there is a large difference of age between husband and wife, the former is generally the older. In our series, there were seven fathers and only one mother who were between 12 and 20 years older than their partner: if these eight were omitted, the difference of the means would be reduced to 2.51 which is not much above the normal figure of 2.3 years, but this normal figure is itself made up of some fathers who are considerably older.

A *paternal* age effect has been shown to operate in achondroplasia, in Marfan's syndrome, and in some forms of acrocephalo-syndactyly (Blank, 1960).

Any correlation between *maternal* age and a congenital malformation is often thought to show that the cause of the malformation is environmental, but equally it may be the factor that reveals a genetically determined defect. The chromosomal anomaly in mongolism that has been demonstrated recently is in most cases closely correlated with advancing maternal age. This correlation and the association between mongolism and congenital heart disease make maternal age worth investigating in congenital heart disease.

The maternal ages at the time of birth of the *propositi* may be compared with (1) a suitable control population (2) the data of the Registrar-General for the general population, or (3) the ages of the mothers at the time of birth of the normal sibs of the *propositi*. The first method is ideal for comparing malformed children born in a particular period and locality with all other children born in the same period and locality; but it is hard to apply to children born in different social groups, in different places, and over a period of several decades. This last point also makes comparison with the Registrar-General's data rather difficult. We have, therefore, used the third method: granted certain assumptions, it can be taken to supply an adequate internal control group.

Birth order is another variable that can influence the occurrence of malformations as, for example, with congenital pyloric stenosis which is common in first-born children, or with a condition such as kernicterus which occurs in later-born children and may have an immunological basis. Its influence can be studied by the same three methods, but in view of its close correlation with maternal age, methods have to be found for separating the respective influences of these two possible factors. We have recently (Campbell and Polani, 1961) given our reasons for using a method based on the work of Greenwood and Yule (1914) and Penrose (1934 and 1946). A series of tables was compiled showing the number of maternities, the birth order, and the maternal age (in five-year periods) for each family. From this, a table was constructed to show the observed and expected numbers for each parity and for each maternal age group, and the sampling variance of these. These last figures enable one to estimate the statistical significance of any numerical differences between the observed and expected values. The results are shown in full in Table III and in shorter and simpler form in Table IV.

Neither maternal age nor birth order are proved to have any influence on the production of atrial septal defect, for the groups with relatively large differences between the observed and expected numbers of cases of atrial septal defect are distributed erratically, and the differences are not statistically significant (greater than twice the square root of the sampling variance). Although the number of cases is larger than those of coarctation, and might therefore be expected to give a more even distribution, there are in fact larger differences in some groups.

Thus, there were 7 less first-born children with atrial septal defect than expected (57 instead of 64) and 6 more second-born children (51 instead of 45), the differences among the later-born children being small, though there was a slight excess among the fifth-born and later (15 instead of 13).

Similarly, there were five less children with atrial septal defect born to mothers of 24 or under (38 instead of 43) and five more born to mothers aged 35-39, (42 instead of 37), but this is not likely to be significant when one less than expected was born to mothers over this age.

The method we have used is not perfect, and the allowance for the fact that every only child in the series must have the malformation sometimes seems to be overweighted. Thus, six of the seven first-born children born to mothers aged 35 or over had atrial septal defect, but they do not seem much more than expected (6 instead of 5.33) because four were only children, two were in two-children families, and only one in a three-children family. Obviously if a first child is born when the mother is over 35, her family is not likely to be very large but it could be larger than these six. Further, many children with atrial septal defect are troublesome in infancy with frequent chest infections: this has no great effect in limiting the size of the family with most mothers, but might with those who are older and so more easily worried by the child. This might cause the older mothers of a first child with atrial septal defect to decide to have no more children. Then, if many

TABLE III

COMPARISON OF 158 PATIENTS WITH ATRIAL SEPTAL DEFECT AND THEIR 349 SIBS WITH RESPECT TO MATERNAL AGE AND BIRTH ORDER

Birth order	Maternal age (in years)						Total
	Up to 20	20-24	25-29	30-34	35-39	40 & over	
1st	1 6 <i>1.5 ± 1.0</i>	24 72 <i>28.0 ± 12.7</i>	20 45 <i>20.8 ± 8.1</i>	6 15 <i>8.5 ± 2.5</i>	6 6 <i>5.0 ± 0.5</i>	0 1 <i>0.3 ± 0.2</i>	57 145 <i>64.1 ± 25.1</i>
2nd	1 3 <i>1.1 ± 0.6</i>	12 38 <i>10.7 ± 6.8</i>	15 40 <i>13.4 ± 8.1</i>	16 31 <i>12.2 ± 6.4</i>	4 10 <i>4.6 ± 2.4</i>	3 5 <i>2.8 ± 1.0</i>	51 127 <i>44.9 ± 25.3</i>
3rd	—	0 8 <i>1.7 ± 1.3</i>	13 40 <i>8.6 ± 6.6</i>	8 24 <i>7.3 ± 4.8</i>	3 24 <i>4.0 ± 2.7</i>	0 3 <i>1.0 ± 0.7</i>	24 88 <i>22.7 ± 16.1</i>
4th	—	0 1 <i>0.1 ± 0.1</i>	2 24 <i>4.5 ± 3.5</i>	7 18 <i>4.2 ± 3.2</i>	1 12 <i>3.0 ± 2.2</i>	1 4 <i>1.1 ± 0.8</i>	11 59 <i>12.9 ± 9.8</i>
5th	—	—	0 6 <i>0.9 ± 0.7</i>	3 18 <i>3.1 ± 2.5</i>	3 8 <i>1.6 ± 1.3</i>	1 2 <i>0.4 ± 0.3</i>	7 34 <i>6.0 ± 4.9</i>
6th and later ..	—	—	0 2 <i>0.2 ± 0.2</i>	2 13 <i>1.7 ± 1.5</i>	4 26 <i>3.5 ± 3.0</i>	2 13 <i>1.8 ± 1.6</i>	8 54 <i>7.2 ± 6.3</i>
All affected cases and all children ..	2 9	36 119	50 157	42 119	21 75	7 28	158 507
Expected affected cases & sampling variance ..	<i>2.6 ± 1.6</i>	<i>40.6 ± 20.8</i>	<i>48.4 ± 27.3</i>	<i>37.0 ± 20.9</i>	<i>21.7 ± 12.2</i>	<i>7.5 ± 4.5</i>	<i>157.7 ± 87.5</i>

The three sets of numbers in each rectangle show: (1) the number of affected children (heavy type), (2) the total number of children at this maternal age and rank, and (3) (below) the expected number of affected children with their sampling variance (in italics).

TABLE IV

DISTRIBUTION OF PATIENTS WITH ATRIAL SEPTAL DEFECT ACCORDING TO MATERNAL AGE AND BIRTH ORDER

Birth order	Maternal age (years)				Total
	Up to 24	25-29	30-34	35 & over	
1st	25 29.6	20 20.9	6 8.5	6 5.3	57 64.3
2nd	13 11.9	15 13.4	16 12.2	7 7.4	51 44.9
3rd	0 1.8	13 8.6	8 7.3	3 4.9	24 22.6
4th	—	2 5.6	7 4.2	2 4.1	11 12.9
5th	—	—	3 3.1	4 2.0	7 6.0
6th and over ..	—	—	2 1.7	6 5.3	8 7.2
Total	38 43.4	50 48.5	42 37.0	28 29.1	158

The figures in heavy type show the number of children observed in each category: the figures in italic, the expected numbers, which are based on a family reconstruction (see text).

mothers did this, the method would fail to show more children with atrial septal defect than expected in this group, even supposing that first-born children born to mothers 35 and over were much more liable to develop atrial septal defect.

Our figures, therefore, still leave open the possibility that first children born to mothers over this age are more likely to have an atrial septal defect than would be expected by chance. Even if this were so, it could only account for a small proportion of the total number with A.S.D., since it is not enough to effect the total expectation for all women aged 35–39 years or for all the first-born children.

VIII. SEX DISTRIBUTION

Atrial septal defect is found more commonly in women than in men—generally in the proportion of about 2:1. Our own 100 cases included 72 women and 28 men, a ratio of 2.6:1, but the ratio varied with age, there being 30 girls and 22 boys under 20, but 42 women and only 6 men over 20: this suggested that the difference in sex incidence might be less at birth but become greater by a differential mortality that was higher in boys and men (Campbell *et al.*, 1957).

From these 100 Guy's patients, we have removed three who had an ostium primum type of defect. The age and sex incidence of the others and of the Middlesex patients are shown first in Table V. To get more information about this, we have asked Dr. Paul Wood, John Goodwin, and Wallace Brigden about their patients and Dr. John Hay and Philip Evans about their experience of A.S.D. in children. We are most grateful to them for the trouble they have taken and for allowing us to make use of details they have given us about their patients. The figures of Wood and Goodwin have been added to Table V. The former include a much larger number at the older ages and show a

TABLE V
SEX AND AGE DISTRIBUTION OF PATIENTS WITH ATRIAL SEPTAL DEFECT*

Age, in year	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 & over	Total
<i>Female patients</i>							
Guy's series	19	10	13	15	9	4	70
Middlesex series	7	16	18	10	8	3	62
Wood's series	32	76	42	33	23	29	235
Goodwin's series	6	19	9	13	9	3	59
Total	64	121	82	71	49	39	426
<i>Male patients</i>							
Guy's series	13	8	2	4	0	0	27
Middlesex series	8	8	9	3	4	2	34
Wood's series	30	61†	23	16	15	17	162
Goodwin's series	6	6	5	5	3	2	27
Total	57	83	39	28	22	21	250
Female/male ratio	1.1	1.5	2.1	2.5	2.2	1.9	1.7

*All patients with an ostium primum type of defect have been excluded.

† 20 referred after X-ray examination for national service have been omitted.

rather smaller female preponderance at all ages: from Wood's figures for the age group 10–19, we have removed 20 men because he wrote that about 30 were young men of 18 or so who had been selected by mass radiography when being considered for their National Service.

Combining these figures the female to male ratio is 1.7 for 676 patients. This ratio is only 1.1 for those up to ten years and then rises to 2.1 in the third decade and stays at about this level at older

ages. Brigden gave us the age and sex incidence of 52 patients he had seen where the diagnosis had been made by mass radiography at work and here too the female preponderance became greater with increasing age—from 1·4 for those under 35 to 1·8 for those over 35 years of age. We have not included these in Table V because there may be selection according to sex when mass radiography is carried out in this way.

This means that women with A.S.D. must see consultants more readily than men or that there is a higher differential mortality in boys and men: this could be because they are less able, or less willing, to adapt themselves to the necessary restrictions in their activity. We have no evidence that there is any such differential mortality. In fact, the only two deaths we have seen in the first two decades of patients with an ostium secundum type of defect were both girls. Wood informs us, that apart from deaths after operation, he has no example of a male patient under 30 dying from uncomplicated A.S.D. and that the male/female sex ratio in those with A.S.D. and the Eisenmenger reaction is considerably higher for women, and this is our experience also. Nor did we find any evidence of differential mortality to account for the sex incidence of persistent ductus and coarctation of the aorta, though a differential mortality in the prenatal or neonatal period was not excluded.

It may seem unlikely that women came to hospital more often than men, but ordinary domestic work has to be carried on and entails the same metabolic consumption of oxygen, and therefore presumably the same work of the heart, as many of the occupations in which men are engaged (Passmore and Durnin, 1955). Men with A.S.D. are less likely to choose the heavier forms of work, so it may be that the woman who has to do housework does more work and is more prone to develop cardiac symptoms from A.S.D. than most men.

We tried to get further evidence about the sex incidence in small children. Hay finds the same female/male ratio of 1·1 for those aged 0–9 (84 F, 75 M) and also for those aged 10–14 years (30 F, 26 M). His findings, however, become more complex if the former are divided into five year periods. Among those 0–4 (a group poorly represented in the figures we have discussed previously) the usual ratio was reversed as there were 30 girls and 35 boys, and for those aged 5–9 there were 54 girls and 40 boys. These figures included *all* the 215 patients with an ostium secundum defect, but a third of those where the diagnosis was proved (37 of 104) had some other cardiac defect as well: in the other 111 there was a provisional clinical diagnosis only. All patients with an ostium primum were excluded. Evans, studying the Great Ormond Street necropsy figures for 1900–43, found only 23 cases with an A.S.D. and no other cardiac malformation: 11 were boys and 12 were girls and 16 of the 23 were under one year of age, so that here again there is no support for a higher male mortality.

The only certain conclusions are that for all ages together the female/male ratio is 1·7 but that for those aged 0–9 years it is nearer 1·1. No decisive explanation for this has been found.

IX. BIRTH-WEIGHT OF PATIENTS WITH A.S.D.

Birth weights of normal children vary widely: they are partly dependent on the economic and social conditions of the family and increase with increasing parity. We have compared the birth weights of our patients with those of their normal sibs as this to a large extent eliminates social class and nutritional factors.

Both the boys and the girls with atrial septal defect were lighter than their normal sibs at birth. The mean birth weight of the boys was $7\cdot36\text{ lb.} \pm 0\cdot19$ instead of $7\cdot78 \pm 0\cdot12$ for their normal brothers, and that of the girls was $7\cdot27 \pm 0\cdot17$ instead of $7\cdot62 \pm 0\cdot14$ lb. for their normal sisters. These differences are of interest but are not large enough to be statistically significant in a sample of this size, even in the boys where the difference was larger.

There was a difference in the distribution of the birth weights (see Table VI) as well as in the lower mean. Rather more of those with an atrial septal defect weighed 5·5 lb. or less (10% instead of 7%) and far less weighed over 8·5 lb. (11% instead of 23%) and this was true both for the boys and for the girls. Children with an atrial septal defect are known to be of lighter weight than normal

TABLE VI

DISTRIBUTION OF BIRTH WEIGHTS OF 129 PATIENTS WITH ATRIAL SEPTAL DEFECT AND THEIR 257 NORMAL SIBS

Birth weight (lb.)	Boys (percentage)		Girls (percentage)	
	With A.S.D.	Sibs	With A.S.D.	Sibs
3.5 and under ..	—	—	1 (1)*	2 (2)*
3.6-4.5	2 (1)*	1 (1)*	4 (3)	2 (2)
4.6-5.5	7 (3)	3 (4)	6 (5)	4 (5)
5.6-6.5	9 (4)	16 (22)	21 (18)	15 (18)
6.6-7.5	52 (22)	30 (42)	35 (30)	32 (39)
7.6-8.5	16 (7)	30 (42)	24 (21)	20 (24)
8.6-9.5	9 (4)	12 (16)	1 (1)	14 (16)
9.6-10.5	5 (2)	4 (6)	6 (5)	8 (9)
10.6-11.5	—	2 (3)	0 (0)	2 (2)
11.6 and over ..	—	2 (3)	2 (2)	1 (1)
No. of cases ..	43	139	86	118
Mean (lb.) and S.E.	7.36±0.19	7.78±0.12	7.27±0.17	7.62±0.14
Standard deviation ..	1.25	1.43	1.55	1.58
Mean (kg.)	3.34	3.53	3.29	3.46

* Figures in brackets give the number of cases.

children, but there is no obvious reason why its presence should cause the child to be lighter at birth, since the effects of an atrial septal defect on the foetal circulation are unimportant.

We analysed the sibs born before and after the propositi separately, but thought it fair to compare the mean of the two groups combined with the mean of those with A.S.D., since we have shown that birth order does not significantly influence the incidence of A.S.D. The boys born after (mean weight, 8.00 lb.) showed the expected increase over those born before (7.58 lb.), but for some reason the girls did not though the difference was small—7.70 lb. for those born before and 7.54 lb. for those born after. Both the girls with A.S.D. and their normal sisters were a little lighter than the boys with A.S.D. and their normal brothers, but the differences were less than the expected mean difference of 0.2 lb.

We have not found any significant difference in birth weights for our patients with persistent ductus (Polani and Campbell, 1960) or with pulmonary valve stenosis (unpublished data)—not even the small decrease found for those with an atrial septal defect—either for boys or for girls. We did find, however, that girls with coarctation were significantly lighter than their normal sisters (6.52 instead of 7.35 lb.) but this was not so for the boys with coarctation.

X. THE SEASONAL INCIDENCE OF BIRTHS

The small differences that we have found in the seasonal incidence of births do not seem to be significant, either for girls or for boys, so this section need be read only by those who might want to compare our findings with series of their own or might be interested in the methods employed. For this reason we have given the births by months as well as by the conventional quarters, although the monthly figures are small. It might seem unreasonable to think of any possible difference between the number of births at different seasons, but girls with persistent ductus were born more frequently from August to October and less frequently from December to March; and boys with coarctation of the aorta were born more frequently from December to July.

The births of our patients with atrial septal defect were spread over a wide period from 1901 to 1951. Because of this wide spread we have thought it best to compare the season of birth of our patients with that of their normal sibs. These are set out by quarters in Table VII and by months

TABLE VII
QUARTERLY INCIDENCE OF BIRTHS OF PATIENTS WITH ATRIAL SEPTAL DEFECT AND THEIR NORMAL SIBS

		January to March	April to June	July to September	October to December
With A.S.D.	Boys (53)	22	12	8	11
	Girls (112)	29	29	28	26
	Total (165)	51	41	36	37
Normal sibs	Boys (178)	49	41	45	43
	Girls (144)	30	43	33	38
	Total (322)	79	84	78	81

in Table VIII. Before the War normal births were rather more common in the second quarter of the year, though up to 1923 the number in the first quarter was sometimes greater than in the second: from 1940 onwards the seasonal incidence of births was unusual because of the disturbed conditions during and for a time after the War. We, therefore, analysed the figures separately for the years 1901–22, 1923–39, and 1940–51 and the figures for these three periods are shown separately in smaller type under the main figures in Table VIII.

Nearly twice as many boys with atrial septal defect were born in the first quarter of the year as in each of the other three quarters. There was no difference in the number of girls with atrial septal defect born in each quarter. Nor was there any significant difference in the number of normal sibs born in each quarter, though curiously there were rather more normal boys and fewer normal girls born in the first quarter.

The larger number of boys with A.S.D. born in the first quarter was due to the unusual number born in January and to a lesser extent in February but this must be of doubtful significance for fewer were born in March and December. The smallest number of boys were born from July to September. More girls were born in May than any other month, but June and July had relatively few births and otherwise they were evenly spaced. None of these differences can be proved to be significant and they may all be due to chance, but it seems worth collecting more data to settle this.

SUMMARY AND CONCLUSIONS

We have made enquiries about the families of 170 patients with atrial septal defect for genetic or environmental factors that might help to explain its aetiology. Many of our patients (16%) had also other malformations of the heart, but generally these were less important. Some had non-cardiac malformations as well.

A congenital malformation of the heart, most often an atrial septal defect, was found more often than would be expected by chance in the sibs of our *propositi* with atrial septal defect (1.1%) and in their parents (1.3%). Many sibs, perhaps more than would be expected, had also non-cardiac malformations (2.1%).

The parents of the *propositi* were first cousins more often than would be expected (1.9%). This suggests that some of the cases are due to recessive Mendelian inheritance. When two members of a family each have an atrial septal defect, they are almost equally likely to be a parent and child or two sibs. In some families there is good evidence of dominant Mendelian inheritance with incomplete penetrance. We think that these two mechanisms could explain only a proportion of cases and that environmental factors also are of importance.

Mean paternal age exceeded mean maternal age by 3.03 years, which is more than the normal difference (2.3 years) and may point to a genetic error, at least in some cases. Neither maternal age nor birth order were proved to have any effect on the incidence of atrial septal defect, but there were several first-born children of mothers of 35 and over and we think this is worth further investigation.

TABLE VIII
THE MONTHLY INCIDENCE OF BIRTHS OF PATIENTS WITH ATRIAL SEPTAL DEFECT AND THEIR NORMAL SIBS

	January	February	March	April	May	June	July	August	September	October	November	December
Boys with A.S.D. (53)	11 0+3+8	7 1+3+3	4 0+2+2	2 2+0+0	5 3+0+2	5 1+2+2	3 1+0+2	2 0+0+2	3 0+1+2	5 1+3+1	3 1+0+2	3 1+2+0
Girls with A.S.D. (112)	9 2+3+4	9 5+2+2	11 6+3+2	9 2+6+1	15 6+6+3	5 1+3+1	6 5+0+1	12 4+3+5	10 2+4+4	10 0+7+3	7 3+2+2	9 3+3+3
Normal boys (178)	21 10+7+4	10 3+4+3	18 6+10+2	19 5+10+4	8 3+3+2	14 5+4+5	9 3+5+1	17 6+6+5	19 9+5+5	11 5+2+4	14 3+4+7	18 10+4+4
Normal girls (144)	10 3+3+4	11 5+3+3	9 1+7+1	14 1+9+4	15 4+2+9	14 2+8+4	8 3+1+4	13 2+8+3	12 2+8+2	11 6+2+3	15 4+6+5	12 6+4+2

The smaller figures below refer to births in the three periods 1901-1922, 1923-1939, and 1940-1951 respectively (see text).

As in most reported series, there were more girls and women than boys and men, the ratio being 1·7:1. The sex incidence was more nearly equal in the first decade, but the reason for this is not clear. Both boys and girls with atrial septal defect were a little lighter at birth than their normal sibs, particularly the boys.

More boys with atrial septal defect were born in January and February and the excess was enough to make the births in the first quarter about double the births in the other three quarters. There was no difference in the quarterly incidence of births for the girls.

We are most grateful to Dr. Evan Bedford for sending out our questionnaire to 94 of his Middlesex patients, and to him and to Dr. Besterman for help in getting more details about some of their answers. We should like to thank also Dr. Wallace Brigden, Philip Evans, John Goodwin, John Hay, and Paul Wood for so kindly giving us information about the age and sex incidence of their patients with atrial septal defect.

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