Papers and Originals

Causes of Malformations of the Heart*

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In 1946, when I began to be interested in malformations of the heart, I thought that situs inversus was inherited as a Mendelian recessive character (Cockayne, 1938), and I had seen a pair of identical twins, both with a ventricular septal defect, and had read of other such pairs. These two aspects pointed to a genetic cause, but the relatively small number of familial cases reported did not readily fit in with this. Six years previously the influence of maternal rubella during the first three months of pregnancy in causing malformations of the heart, often with cataract and deafness, proved the importance of environmental causes. Further experience has, however, shown that only a small proportion, no more than 2%, of malformations of the heart can be attributed with reasonable certainty to this cause, and careful investigations of the influence of other infections have done no more than show that these may be the source of occasional cases (Campbell, 1961a).

The relative importance of genetic and environmental factors in malformations of the heart was discussed shortly on the experience of my first 300 cases (Campbell, 1949). This led to the study by Polani and Campbell (1955) on the families of (i) 300 cyanotic children, mostly with Fallot's tetralogy, and 84 acyanotic children who have been excluded now as they are included in our later groups. Since then we have thought it would be better to study homogeneous groups, and have extended our studies to the families of (ii) 261 patients with persistent ductus arteriosus (Polani and Campbell, 1960); (iii) 151 with coarctation of the aorta and (iv) 170 with atrial septal defect (Campbell and Polani, 1961a, 1961b); (v) 125 patients with pulmonary stenosis and (vi) 40 with complete or partial situs inversus (Campbell, 1962, 1963); and (vii) 180 with ventricular septal defect (Campbell and Goodwin, 1965). In this paper I shall compare our findings in these 1,227 patients (891 acyanotic and 336 cyanotic) with other reported series and see what general conclusions can be drawn.

The relative importance of genetic and environmental factors in the production of malformations of the heart is still a long way from being understood. Herndon, in his chapter on cardiovascular diseases in Sorsby's *Clinical Genetics* (1953), covers the ground in three pages, while 18 pages are given to diseases of the eye; and family trees showing affected members in several generations are vastly more common in the latter group. Not much has been added since then about malformations of the heart, though the advances in human genetics have been enormous, as shown by the greater knowledge of the human chromosomes and their correct enumeration, and by the discoveries about mongolism and ovarian dysgenesis, to quote only two instances.

At the First International Conference on Congenital Malformations, held in London in July 1960, and at the Conference on Clinical Aspects of Genetics, held at the Royal College of Physicians of London in March 1961, less was said about malformations of the heart than about most other important groups, though numerically they are as important as any and account for about a quarter of the major malformations.

Incidence of Malformations, Especially Those of the Heart

An estimate of the *incidence of all common congenital malformations* will be needed as a standard for comparison with the findings in our families. This has been considered recently by McKeown and Record (1960) and by Carter (1961): they base their conclusions mainly on three recent series from England, America, and Japan; and in my final estimate of a figure double weighting has been given to the British figures, as the comparisons to be made will be with British families. In these series the total incidence of all major malformations is 2.4%, and malformations of the heart form one-quarter of these—that is, 0.6%.

The incidence of *all malformations of the heart* was as low as 2 per 1,000 in many of the older series. The first attempt to estimate this on a large scale by means of the improved methods of diagnosis was made by MacMahon *et al.* (1953), who found it 3.2 per 1,000. Since then the question has been looked at more carefully and a higher figure has been generally accepted. Harris and Steinberg (1954) found it 6.8, McIntosh *et al.* (1954) found it 6.5—both these authors in America—and Carlgren (1959) found it 6.4 per 1,000 in Sweden. For purposes of comparison I have accepted the figure of 6 per 1,000, and a similar figure was given by McKeown and Record (1960) and by Carter (1961). The incidence of all malformations, of all those of the heart, and of those of the different forms of malformations of the heart is only summarized shortly here but will be dealt with more completely (Campbell, 1966).

The incidence of the specific malformations of the heart at birth is not yet certain because of the difficulties of early diagnosis. On the present evidence ventricular septal defect (V.S.D.) seems to form about 20% of the total, but this may be too high an estimate; then persistent ductus arteriosus (P.D.A.), atrial septal defect (A.S.D.), coarctation of the aorta, pulmonary stenosis (generally valvular, P.V.S.), Fallot's tetralogy, and transposition of the great trunks are each responsible for about 10%, and aortic stenosis for about 5%; this makes 85% of the total, leaving 15% for all the many less common malformations. With a total incidence of 6 per 1,000 this means that the incidence of most groups (P.D.A., A.S.D., etc.) is about 0.6 per 1,000, of V.S.D. much more than this, and of aortic stenosis about half of this.

Their distribution among older children shows some striking differences because of the very heavy early mortality, especially in the first year of life. Transposition ceases to form a significant proportion because of its extremely high mortality, and V.S.D. and coarctation become less prominent. Roughly speaking, the position in older children can be summarized as

* Based on papers given at the Boerhaave Cursus, Leyden, Holland, in April 1963, and at the Johns Hopkins Hospital, Baltimore, in March 1964.

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V.S.D., A.S.D., P.D.A., and P.V.S., each forming about 15% of the total, Fallot's tetralogy 12%, and coarctation and aortic stenosis each 6%, leaving 16% for all the other less common malformations.

The incidence of all malformations of the heart will therefore be lower in the general population of older children. If we assume an early mortality of 40%, it will be 3.6 instead of 6 per 1,000, and the incidence of each of the commoner malformations of the heart will be about 0.5 per 1,000. For A.S.D. this is more than twice as high as the 0.2 per 1,000 found by Seldon *et al.* (1962) among the Australian population aged 15–65, which would be about the right relationship to allow for the increasing deaths from A.S.D. after the fourth decade.

Other Malformations in Propositi with Malformations of the Heart

Other Cardiac Malformations.—When a patient has one malformation of the heart he is more liable than others to have a second one. The proportion varied from 8% in our group with coarctation to 15% of those with A.S.D. and 21% with P.V.S. (see Table I). The average figure for all our acyanotic groups was 13%, about 20 times the expected figure. This includes some well-known associations—for example, aortic stenosis or P.D.A. with coarctation—but excludes the two malformations that must be present in most cyanotic malformations—for example, V.S.D. and P.V.S. in Fallot's tetralogy.

Non-cardiac Malformations.—With a malformation of the heart there is often a non-cardiac malformation also, and this may be of almost any type. It is generally agreed that the combination occurs much more often than would be expected by chance. In our different groups the proportion so affected varied from 5% in A.S.D. to 13% in coarctation and P.V.S., and averaged 9% (Table I). The method of selection inevitably makes this a low figure, as patients investigated were generally thought suitable for operation, and, for example, few mongols were included. In the series of Lamy *et al.* (1957) the figure was 16%, and varied between 7% and 26% in their different groups. MacMahon *et al.* (1953) found it as high as 20.7% in 488 cases.

No one group of malformations of the heart was more liable to be associated with a non-cardiac malformation than others in both these series. The combined figures for each group separately in our series and in that of Lamy *et al.* evened out and were all between 10% and 15%, and the average for both series for all groups was 12%—nearly five times as much as would be expected by chance. Wood (1956) says that other malformations are present in from 10% to 20%, the lower figure in clinical series and the higher one in those with a necropsy.

Malformations in Sibs of Propositi

Cardiac Malformations

All our groups showed an increased incidence of cardiac malformations in sibs of the propositi, except coarctation of the aorta, where only 0.4% of the sibs had such a malformation. The proportion varied from 1.1% in A.S.D. to 2.7% in Fallot's tetralogy (Table I), with an average of 1.7% (including coarctation). In the similar series of Lamy *et al.* (1957) it was the same, 1.7%, and also in the series of McKeown *et al.* (1953), where it was 1.8% in the sibs born after the propositi. In the series of Fuhrmann (1961) it was higher, 2.7%. Our figure is three times as high as would be expected by chance, and we may have failed to find some of the cardiac malformations that had caused death in infancy.

If our figures are combined with those of Lamy *et al.* for each separate group the low figures for coarctation in our series and for V.S.D. in theirs are both balanced by higher figures in the other series. The percentage for each combined group lay between 1.1 for V.S.D. and A.S.D. and 1.9 for Fallot's tetralogy, except for P.V.S., where it was 2.8; the average for all the groups was 1.7%. Zoethout *et al.* (1964) have made similar inquiries about 126 subjects with congenital aortic stenosis. They found 4% of the sibs had malformations of the heart, most often the same as in the propositi. We are uncertain if the figures are large enough to say that the incidence of malformations of the heart in sibs is really more in the P.V.S. and aortic stenosis groups, but there can be no doubt that it is generally increased in all the groups.

There is a strong tendency for the malformations found in the sibs to be *concordant* with those in the propositi, and the concordance or discordance of the malformations is shown in Table II. Among our 34 examples the concordance was com-

TABLE I.—*Percentages of Malformations in the Propositi with Malformations of the Heart and their Families*

Primary Malformations in Propositi:		Percentages Affected in Each Group					
		P.D.A.	A.S.D.	V.S.D.	Coarct.	P.V.S.	Fallot‡
Other malformations in propositi	Cardiac*	10	15	11	8	21	All
	Non-cardiac	6 (16)†	6 (26)	8 (14)	13 (7)	13 (16)	6 (15)
Malformations in sibs	Cardiac	2·1 (1·2)	1·1 (1·2)	1·7 (0·5)	0·4 (2·6)	2·1 (3·7)	2·7 (1·0)
	Non-cardiac	2·0	2·1	3·1	2·8	1·5	2·1
Malformations in parents	Cardiac	0·8	1·3	0	0·7	0	0·2
	Non-cardiac	1·2	1·0	0·6	0·7	0	0·5

* This refers to a second cardiac malformation in the propositi, and rather more than half the second malformations in subjects with V.S.D. were P.V.S.; and in those with P.V.S. were V.S.D. All subjects with Fallot's tetralogy have, of course, a V.S.D. and pulmonary stenosis.
† The figures in parentheses are those given by Lamy *et al.* (1957).
‡ Groups 1 and 2 of Polani and Campbell (1955).

TABLE II.—*Concordance or Discordance of Malformations of the Heart in Propositi and their Sibs*

Primary Malformation of Propositi	Total No. of Families	No. of Malformations in Sibs				Sibs Affected		Percentage of Sibs Affected (Lamy *et al.*)	Concordant (Lamy *et al.*)
		Completely Concordant	Partly Concordant	Not Concordant	Not Known	No.	%		
Coarctation	151	1	0	0	0	1	0·4	2·6	1 of 2
P.D.A.	261	6	0	2†	1	9	2·1	1·2	0 of 3
P.V.S.	125	3	3*	0	0	6	2·1	3·7	1 of 2
A.S.D.	170	2	0	0	2	4	1·1	1·2	1 of 2
V.S.D.	180	1	1*	2†	2	6	3·3	0·5	1 of 2
Fallot's tetralogy§ (groups 1 and 2)	300	2	2*	2†	2‡	8	2·7	1·0	2 of 4
Total	1,187	15	6	6	7	34	1·7	1·7	6 of 15

* The partly concordant malformations are Fallot's tetralogy in 3 sibs of propositi with P.V.S. and in 1 with V.S.D.; and P.V.S. in 2 sibs of propositi with Fallot's tetralogy.
† The non-concordant malformations are V.S.D. and aortic stenosis (in sibs of propositi with P.D.A.), dextrocardia and anomalous pulmonary venous drainage with A.S.D. (in sibs of those with V.S.D.), and transposition twice (in Fallot's tetralogy).
‡ Both cyanotic.
§ These 300 are the cases of groups 1 and 2 (Polani and Campbell, 1955).

plete in 15, partial in 6, absent (discordant) in only 6, and unknown in the remaining 7, in whom the nature of the malformation in the second of the pair was not known. Partially concordant means an example of P.V.S. or V.S.D. in a sib of a propositus with Fallot's tetralogy, or Fallot's tetralogy in a sib of a propositus with P.V.S. or V.S.D. In the similar series of Lamy *et al.* (1957) there was complete concordance in six, partial concordance in one, discordance in two, and unspecified in six, this last being the only reasons for the apparently lower incidence of concordance. McKeown *et al.* (1953) found five pairs of sibs in whom both were affected: in three the malformations were concordant (pairs with P.D.A., V.S.D., and transposition of the great vessels), in one they were partially concordant (Fallot's tetralogy and V.S.D.), and in only one were they discordant (P.D.A. and transposition). Fuhrmann (1961), from his own and reported cases, thought that pairs were nearly always concordant, but Neill (personal communication) finds less concordance at the Johns Hopkins Hospital, Baltimore.

In summary, where a sib also has a malformation of the heart that has been diagnosed it is concordant with that in the propositus in six (56%), partially so in two (22%), and discordant in only two (22%) of each ten cases. The chance expectations of a sib having any such malformation of the heart is 0.6% against the 1.7% actually found, and of his having the same malformation by chance is only 0.06% (less for the less common varieties) against the 0.95% found.

The number of malformations of the heart is therefore three times as many as would be expected, and the same malformation is found 15 to 20 times as often as would be expected by chance, other malformations being found about as often as would be expected.

Non-cardiac Malformations

The number of these non-cardiac malformations in the sibs of the propositi of our various groups lay between 1.5% (in P.V.S.) and 3.1% (in V.S.D.), with an average of 2.3%. This is about the percentage of major malformations present in the general population, so there is no evidence of the special liability to non-cardiac malformations that was found with the propositi themselves. Lamy *et al.* (1957) came to the same conclusion, since the incidence was 1.0% in the sibs of their propositi and 1.1% in their controls. MacMahon *et al.* (1953) also found no increase.

Malformations in Other Relatives

Malformations in Parents

In general there was no tendency to malformations of the heart in the parents. The incidence found in all our groups except A.S.D. averaged 0.3%. This is less than the general incidence, as might be expected, since many parents with malformations would be less likely to marry and have children. Only the fathers and mothers of propositi with A.S.D. had a cardiac malformation more often than would be expected by chance; and when they had, it was always an A.S.D. Four parents (1.3%) and perhaps three others had an A.S.D.; even excluding the last three this is more than would be expected with any cardiac malformation, and far more than would be expected with A.S.D. Details of a family with four members in two generations with proved A.S.D. and four others in three earlier generations who probably had an A.S.D. were given by Campbell and Polani (1961b), and they referred to some other reported families with similar histories. Since then Weil and Allenstein (1961) have reported one where a father and four of his 11 children had proved A.S.D.

It seems almost certain, therefore, that in a few families A.S.D. is inherited as a dominant autosomal gene without complete penetrance (Campbell and Polani, 1961b), but this can apply to only a few of the families with A.S.D. I regret that I have not found the time to make similar inquiries about the families of patients with congenital aortic stenosis, because I have seen a mother and son with this, where her father and uncle were thought to have the same condition; two brothers and in another family two sisters, all with congenital aortic stenosis (Campbell, 1959); and a boy aged 16 with congenital aortic stenosis, whose first cousin died when 11, probably with the same condition. Here too there may be a relatively high proportion of familial cases, though Zoethout *et al.* (1964) found no example of an affected parent.

In the other groups only 0.3% of the parents had any cardiac malformation, and this is no more than would be expected by chance. This was true for non-cardiac malformations also, where only 0.7% were known to be affected.

Malformations in Children of Propositi

Owing to the youthful age of most of the propositi we have not much information about this tendency. Of the 90 children about whom we know four were affected—a son of a propositus with Fallot's tetralogy, who had a persistent ductus; a son of one with coarctation, who had pulmonary stenosis; and two children of propositi with A.S.D., of whom one died with congenital heart disease and the other probably had an A.S.D. The same percentage of the children had non-cardiac malformations.

These proportions of 4.4% are higher than would be expected by chance, especially for cardiac malformations. The numbers are too small for any decisive conclusion, but show that the subject is worth investigation on a larger scale, though it may prove to be normal for all except perhaps A.S.D.

Malformations in Less Close Relatives

Several malformations, cardiac and non-cardiac, were reported in uncles, aunts, and first cousins, but we do not know the number at risk. If they were, as might be expected, in families of average size they did not seem to be significantly increased. As an exception the propositus with A.S.D. has two first cousins with proved A.S.D., one first cousin who had a successful operation for Fallot's tetralogy, and two first cousins who died young with some form of congenital heart disease. Lamy *et al.* (1957) found some increase of cardiac malformations in first cousins.

Consanguinity of Parents of Propositi

A high proportion of marriages between first cousins points to inheritance through a recessive gene, and this was the main evidence that complete situs inversus was inherited in this way (Cockayne, 1938). In our patients with complete or partial situs inversus there had been cousin marriages between 2 of the 38; and in the 379 cases that were collected, mostly from Torgersen (1946, 1950), there were first-cousin marriages between the parents of 5.3% (Campbell, 1963). This is 11 times as high as the level in the general population of Britain. I have taken this level as 0.5%: it has been estimated as between 0.4% (Bell, 1940) and 0.6% (Roberts, 1955), but the latter thinks it is now more likely to be between 0.4% and 0.5%.

The percentage of cousin marriages in our other groups and the index of consanguinity from our figures and those of Lamy *et al.* (1957) are shown in Table III. The percentage of first-cousin marriages was 1.1%, at least twice the expected figure. Lamy *et al.* (1957), in France, and Fuhrmann (1961), in Germany, also found it increased, the latter to 1.7% and the former to a higher figure of 2.5%, but their figure of 0.7%

for the French controls was higher also. Our figure of 1.1% for first-cousin marriages, excluding those with situs inversus, suggests that recessive inheritance is the cause of some cases or a predisposing condition for more of them.

TABLE III.—*Consanguinity of Parents of Propositi with Malformations of the Heart*

	Percentage of Parents Who Were Cousins (Campbell, present series)		Index of Consanguinity		
	1st Cousins	2nd Cousins	Campbell (present series)	Lamy *et al.* (1957)	Mean
P.D.A. ..	1·6	0	1·6	2·3	1·9
A.S.D. ..	1·9	1·9	2·4	3·8	3·1
V.S.D. ..	1·2	0·8	1·4	0·9	1·2
Coarctation	0	0	0	0·6	0·3
P.V.S. ..	0·9	0	0·9	4·5	2·7
Fallot's ..	0·8	0·8	1·0	0·1	0·6
Mean ..	1·1	0·6	1·2	2·0	1·6
Normal ..	0·4–0·5	—	—	0·7	—
Situs inversus..	5·3*	1·3*	5·6	14·3	—

* These are taken from 379 families, and include reported as well as personal cases (Campbell, 1963).

As usual, our figures for each individual malformation (Table III) cannot be as reliable as for the combined groups, since the numbers involved are smaller. Even so it seems worth mentioning that we found no first-cousin marriages in our families with coarctation of the aorta: Lamy *et al.* also found the lowest incidence, just below their normal controls, in this group. We feel no confidence that this low figure of 0.3% for coarctation means that recessive inheritance is without significance for coarctation, and larger numbers will be needed to settle this. If it were so, and this group were omitted, the percentage of first-cousin marriages among all the other groups combined would be rather higher. Taking the mean of the coefficient of consanguinity given by Lamy *et al.*, and a simpler coefficient for my findings (adding one-quarter for each second-cousin marriage to one for each first-cousin marriage), the incidence is lowest for coarctation (0.3%) and next lowest for Fallot's tetralogy (0.6%). V.S.D. (1.2%) is just below the mean of 1.6% and P.D.A. (1.9%) just above it. P.V.S. (2.7%, almost entirely because of Lamy's high figure) and A.S.D. (3.1%) have the highest index of consanguinity except for situs inversus. These findings are based on over 2,000 cases, but, even so, we feel they need confirmation from additional series.

Parental Age and Birth Order

We have found no evidence that *birth order* alone has any general influence on the production of malformations of the heart. Lamy *et al.*, however, found that, if maternal age was held constant, birth rank was significantly higher in the C.H.D. group than in controls for the maternal age groups 25–29 and 30–34. MacMahon (1952) found some evidence that third-born children were more liable to malformations of the heart, and that P.D.A. was more common in first-born children, but this has not been confirmed subsequently. In our series the only significant finding about birth order was linked with maternal age, and more sixth and later children with V.S.D. were born to mothers aged 35–39.

Maternal age was rather more important, though the mean ages of all the mothers in each group was not any greater than would be expected (between 28.47 and 29.35 years). Only in Fallot's tetralogy and V.S.D. did maternal age have an influence that was statistically significant. More children with Fallot's tetralogy were born to mothers aged 40 to 45 years, after children with mongolism were excluded because of the known influence of maternal age in this condition. Significantly more sixth and later children with V.S.D. were born to mothers aged 35 to 39, and the excess of sixth and later children born to mothers aged 35 and over only just failed to reach the level of significance.

In the A.S.D. group rather more children were born to mothers of 35 and over, and in the P.V.S. group more to mothers of this age group, especially when they were fourth-born or later children; but neither of these increases was statistically significant. MacMahon (1952) also thought that septal defects were more common among the children of older mothers. In our V.S.D. group there was some evidence that older mothers were more likely to have an affected child when there had been no previous pregnancy or had been a long interval since the last one, and in our coarctation group affected children seemed more common at the end of a large family when the mother was getting older; but it was difficult to prove that these were statistically significant. In all our groups mongols had been excluded. Only in our P.D.A. group was there no suggestion of any greater liability of older mothers to have an affected child, but the excess was statistically significant only in the V.S.D. and Fallot's tetralogy groups.

Penrose (1955) pointed out that the difference between the *means of the paternal and maternal ages* are in some ways a more useful measurement, since an undue increase of the paternal age suggests the possibility of a "failure to copy genes correctly" because of the larger number of cell divisions in the male-germ line. The mean paternal age exceeded the mean maternal age by more than the 2.3 years expected from the general population (Penrose, 1957), and ranged from 2.87 in coarctation and 3.03 in A.S.D. to 3.48 in P.V.S. and 3.70 in V.S.D. (see Table IV). These increases are suggestive, but much less than those found in achondroplasia, 5.6 (Penrose, 1957) and 7.2 years (Stevenson, 1957)—a condition that is recognized as generally due to a dominant gene mutation influenced by high paternal age.

TABLE IV.—*Mean Year of Marriage and Mean Ages of Fathers and Mothers of Propositi with Malformations of the Heart*

	Mean Year of Marriage of Parents	Mean Paternal Age (Years)	Mean Maternal Age (Years)	Excess of Paternal Age Over Maternal Age (Years)	
				Parents of Propositi*	Normal Controls
P.D.A. ..	1934	31·96	28·65	3·31 (117%)	2·83 (2·66)
A.S.D. ..	1925	32·08	29·05	3·03 (117%)	2·58 (2·51)
V.S.D. ..	1938	32·93	29·23	3·70 (125%)	2·96 (2·80)
Coarctation ..	1930	31·34	28·47	2·87 (106%)	2·70 (2·58)
P.V.S. ..	1931	32·83	29·35	3·48 (127%)	2·73 (2·60)
Fallot's tetralogy ..	1934	32·57	29·35	3·22 (121%)	2·66 (2·66)
Average ..	—	32·29	29·02	3·27 (119%)	2·74 (2·64)

* The figures in parentheses show the excess paternal age as a percentage of what might be expected in the general population (in sixth column).

I have, however, become less satisfied with the use of 2.3 years as the normal excess of mean paternal over mean maternal age, because the excess in the general population has been increasing from 2.17 years in 1906–10 to 3.0 years in 1951–5 (Registrar-General, 1957). The marriages involved in my cases were spread over a wide period from 1893 to 1948, and the question is to decide what level between these extremes should be used. The mean year of marriage of the parents of our V.S.D. patients was 1938, with a skew distribution, and the largest number of marriages in 1941–5. About half the V.S.D. patients were collected five years later than all the others, and they also tended to be younger. I was sure, therefore, that the mean year of the parental marriages in my other groups was about five years earlier and probably still earlier for A.S.D. and coarctation, as these groups included more older patients.

When the mean year of parental marriages was worked out my estimate proved conservative, and the years were 1934 for P.D.A. and for Fallot's tetralogy, 1931 for P.V.S., 1930 for coarctation, and as early as 1925 for A.S.D. (see Table IV). From the Registrar-General's data the mean excess for each of these years can be calculated, and these figures are shown in parentheses in the sixth column of Table IV. To make sure that I am not claiming a higher excess than is justified, five

years has been added to the mean year of marriage to allow for the skew distribution and the larger number of marriages that took place in the five years after the mean, except for Fallot's tetralogy, where there was not the same skew distribution. These figures are shown first in the sixth column and have been used for comparison.

In every group the excess of mean paternal over mean maternal age is greater than that found in the general population at the time. It is least (6%) and probably not significant for coarctation of the aorta, 17% or more in all others, and largest (21% to 27%) for P.V.S., V.S.D., and Fallot's tetralogy.

Lamy *et al.* (1957) found the fathers a little older and the mothers a little younger in their C.H.D. group than in the controls: neither of these differences alone was significant, but the excess of the mean paternal age, 2.90 against 1.94 years in their French controls, was significant. These differences in our groups and in those of Lamy *et al.* are therefore suggestive of a genetic factor.

Birth Weight

Both boys and girls with V.S.D. and girls (but not boys) with coarctation of the aorta were a good deal lighter than their normal sibs of the same sex (Table V). The mean weight of the boys with V.S.D. was significantly lighter than their normal brothers—7.16 ± 0.14 compared with 7.86 ± 0.12 lb. The lighter mean weight of the girls with V.S.D. only just failed to reach the level of significance—6.86 ± 0.15 compared with 7.36 ± 0.11 lb.

TABLE V.—*Birth Weight (lb.) of Propositi with Malformations of the Heart and Their Normal Sibs*

	Boys		Girls	
	Affected	Normal	Affected	Normal
No significant difference between affected and normal				
P.D.A. ..	7·56 ± 0·17	—	7·36 ± 0·11	—
A.S.D. ..	7·36 ± 0·19	7·78 ± 0·12	7·27 ± 0·17	7·62 ± 0·14
P.V.S. ..	7·40 ± 0·26	7·57 ± 0·13	7·13 ± 0·22	7·00 ± 0·18
Coarctation ..	7·70 ± 0·19	7·78 ± 0·14	—	—
Mean	7·51	7·71	7·27	7·31
Affected children significantly lighter				
Coarctation ..	—	—	6·52 ± 0·25*	7·36 ± 0·13
V.S.D. ..	7·16 ± 0·14	7·86 ± 0·12	6·86 ± 0·15	7·36 ± 0·11

* Excluding those with Turner's syndrome, 6·69 ± 0·24.

The girls with coarctation were significantly lighter than their normal sisters—6.52 against 7.36 lb. Coarctation has some association with Turner's syndrome, and children with this are often unusually light at birth. This, however, was not the whole explanation, since when the three cases with Turner's syndrome were removed the mean weight of the remaining girls with coarctation was 6.69 ± 0.24 against 7.36 ± 0.13 lb.

In all these three groups there was a larger proportion of children whose weight at birth was less than 5½ lb. (2.5 kg.), and a smaller proportion weighing more than 8½ lb. (4 kg.). Several malformations occur more often in children with a low birth weight, but the significance of the light weight in these two cardiac conditions is uncertain. A comparison with their normal sibs was thought the best way of avoiding the effects of social and environmental factors on birth weight. Sibs born before and after the propositi were analysed separately, and, as expected, the latter were rather heavier; but these were combined for the comparison, since birth rank had little, if any, influence on the production of these malformations.

There was nothing remarkable about the birth weights of the children in our other groups, though later on during childhood most of them were below normal weight and in some groups below normal height. The propositi in each group were a little lighter than their normal sibs (boys than brothers and girls than sisters), but the differences were not of statistical significance. Excluding the three groups discussed, the mean weight of the affected boys was 7.51 against 7.71 lb. for their normal brothers; and of the girls, 7.27 against 7.31 lb. for their normal sisters. The girls were thus lighter than the boys by about the normal amount. No information was obtained about the birth weights of infants with Fallot's tetralogy.

Seasonal Incidence of Births

The season of conception provides some environmental factors that may have an influence on the causation of malformations, but it is easier to talk about the season of birth. Normal children are born fairly regularly throughout the year, but not quite so—26.8% being born in March to May, 25.3% in June to August, 23.7% in September to November, and 24.2% in December to February (Registrar-General, 1957). McKeown and Record (1951) and Edwards (1958) found that births of patients with anencephaly were more frequent in the two winter quarters. Congenital dislocation of the hip shows more births in the winter months (Record and Edwards, 1958). Rutstein *et al.* (1952), in America, found a concentration of births of subjects with P.D.A. from October to January. Record and McKeown (1953), in Birmingham, found a seasonal increase of P.D.A. for girls, but not for boys, from May to December, with a peak in July and August.

Our figures agree with those of the last authors in showing a similar concentration for girls and not for boys, though our peak was from August to November, and fewer were born in December, January, and March. To get a larger number of British figures we have combined ours with those of Record and McKeown: then more affected *girls* were born from May to November, with a peak in August, and fewer from December to April; affected *boys* were distributed more equally throughout the year, though rather fewer were born from January to March.

We have found a varying seasonal incidence in some other groups, though the figures are not large enough to make this certain. With coarctation of the aorta, more boys were born in March and April and fewer in September and October: as they were much more numerous, in the combined figures they overweighted the girls, who showed an exactly opposite trend. With P.V.S., three times as many boys were born in the July–September quarter as in the April–June quarter, but the girls were more evenly distributed. With A.S.D., nearly twice as many boys were born in the January–March quarter as in any of the other quarters, and again the girls were more evenly distributed.

The findings for subjects with a persistent ductus are based on larger numbers and are in general agreement for two series, so are probably correct. The findings in the other groups are interesting but need confirmation from other series.

Sex Incidence of Malformations of the Heart

The different distribution of the two sexes in so many common malformations of the heart has been recognized for a long time. Most works give the distribution among children and young adults rather than the true incidence at birth. The little that is known about this comes mainly from the series of MacMahon *et al.* (1953) and of Carlgren (1959), and will be dealt with first. The two series agree reasonably well, and what follows is based on their combined results.

P.D.A. is the only common condition where there are more girl than boy infants, the male incidence being only 40% of the total. A.S.D. and coarctation show an equal incidence in the two sexes. All others show an excess of boys, but it is small for aortic stenosis and pulmonary stenosis, the boys forming 55%. V.S.D. and Fallot's tetralogy have a higher

male incidence of 59–61%, and transposition has the highest with 73%.

TABLE VI.—*Sex Incidence at Birth and Later*

Condition	Percentage of Male Subjects		
	At Birth (MacMahon *et al.* and Carlgren)	Children 0–15 (Keith *et al.*)	Children, Mostly Over 5, and Adults (Campbell)
P.D.A.	40	31	27
A.S.D.	50	40	34
Coarctation	50	65	62
Aortic stenosis	55	60	70
Pulmonary stenosis	55	—	50
V.S.D.	59	(50)*	30*
Fallot's tetralogy	61	60	59
Transposition	73	68	—

* No figure was found in Keith *et al.* for pulmonary stenosis or V.S.D. The figure given in parentheses is from Campbell for those under 20, and the figure in his column is for those over 20 years of age.

The distribution in the series of Keith *et al.* (1958) is taken next because it consists of children up to 14 with many seen soon after birth. P.D.A. has an even lower male percentage of 31. In A.S.D. the male percentage has fallen to 40, and in coarctation it has increased to 65. It has increased for aortic stenosis also, but only from 55 to 60. Unfortunately I cannot find any figures for pulmonary stenosis and V.S.D. For Fallot's tetralogy there is no change, and there is still the same high male distribution for transposition (68%).

My own figures, which include many young adults and many fewer children under 5, continue and confirm most of the trends shown by Keith's figures. The proportion of male subjects with P.D.A. is still lower (27%), so is that for A.S.D. (34%), while for coarctation it is much the same (62%). For aortic stenosis it has become much higher (70%). Pulmonary stenosis shows an equal distribution between the two sexes; and Fallot's tetralogy shows the same male excess. V.S.D. has reversed the male excess at birth (59%) considerably; Brotmacher and Campbell (1958) found it almost equal in children, but over 20 years of age only 30% were male.

To summarize, P.D.A. is the only condition more common in the female sex at birth and through life. Pulmonary stenosis shows an equal incidence in both sexes; and transposition (70%) and Fallot's tetralogy (60%) show excesses of male cases: none of these three show any differential mortality after infancy. The conclusion of Brotmacher and Campbell (1958) that the mortality of boys with V.S.D. is higher than that of girls has been confirmed by a recent series of 180 cases where the boys still living were 58% among those born since 1940 and only 27% among those born before 1940, and also by the larger number of boys with V.S.D. at birth. They found that boys reversed the left-to-right shunt at an earlier age than girls, and became cyanotic and died earlier; and suggested that this might be because boys are less willing to limit their exertion to an appropriate standard.

This is probably the reason for the higher differential mortality of boys with A.S.D. Campbell and Polani (1961b), on their own and collected cases, found that the sex distribution was about equal in the first decade (and this has been found at birth also), but in the third decade and after the female/male ratio rose to 2:1 and remained at that level, which is about the figure that is generally accepted, though the equal incidence earlier is less widely known. Possibly there is a similar but smaller excess male mortality for P.D.A. in early life, but there is no evidence of this in older children and in adults (Campbell, 1955).

Coarctation shows an equal incidence at birth, and aortic stenosis only a small male excess (55%). In older children and adults there is wide agreement that the incidence in male subjects is 60% or more, though my own experience of 70% may be rather high. Campbell and Baylis (1956) found no evidence of a higher differential mortality in girls with coarctation, nor have I with aortic stenosis: though such a differential mortality seems unlikely, it is not easy to see any other explanation.

Professor Polani has suggested to me that the higher mortality in girls with coarctation might be due to the association with Turner's syndrome. This has an incidence of about 1 in 3,000. If we assume that half these girls have also coarctation, and that this has an incidence at birth of 1 in 2,000 in both sexes, it would be made up as follows: 1 in 6,000 girls with Turner's syndrome and coarctation, 1 in 3,000 girls with coarctation alone (making 1 in 2,000 girls), and 1 in 2,000 boys.

The mortality in the neonatal period is known to be high; if it continued high for girls with coarctation and Turner's syndrome, and if half of them died in the first decade, this would explain the increasing male frequency. The very high prenatal mortality of Turner's syndrome would, however, demand a higher incidence of female cases in early pregnancy.

More certain figures for the sex incidences of all the common malformations of the heart are needed urgently; and also for their prenatal differential mortality. There is no evidence that they are sex-linked in the genetic sense; but the different sex incidence at birth of many cardiac, and some other, malformations is so striking that it might provide a valuable clue to their aetiology, unless it can be explained entirely by a different prenatal mortality between the sexes, and this does not seem very likely.

We have presented some of the findings that have to be explained by any hypothesis about the causes of malformations of the heart. It seems best to consider the evidence for genetic and environmental causes separately, though some combination of these two factors is generally more important than either acting alone. First, we shall discuss certain abnormalities of the chromosome and, where pertinent, some of the evidence that can be added from experimental work on animals.

Abnormalities of the Chromosome

Trisomy.—Mongolism, as is well known, is caused by trisomy of chromosome 21. It is so often accompanied by malformations of the heart, especially septal defects, that these too must be caused, in part at least, by the trisomy. More recently two other pertinent syndromes caused by trisomy, with multiple malformations, including most often V.S.D., have been described. In one, E_1 or chromosome 17–18 (probably 18) trisomy, retarded development, hypertonicity, a flexion-deformity of the fingers, a small mandible, low-set and malformed ears, and malformations of the heart were almost constant findings. In the second, D_1 or chromosome 13–15 trisomy, retarded development, deafness, defects of the eye and brain, hare-lip and cleft palate, malformed ears, polydactyly, and malformations of the heart were common. A V.S.D. was present in 20 out of 22 cases of the former syndrome at necropsy, and in 9 out of 15 cases of the latter syndrome (Taylor and Polani, 1964; Campbell and Goodwin, 1965). Neither of these is likely to be the cause of many cases of clinical V.S.D., since few of the subjects with them survive infancy; but they show that V.S.D. and other malformations of the heart can be produced by trisomy of a chromosome.

Sex Chromosomes.—The association of Turner's syndrome with coarctation of the aorta (Campbell and Polani, 1961a) suggests that it too may be due to the abnormal XO chromosome complement. Sometimes, but not as often as with coarctation, other cardiac malformations may be found with Turner's syndrome, so they too may sometimes be caused in this way.

Genetic Causes

Dominant Mendelian inheritance seems to be of no general importance but to be the main cause of a few small groups. In

a few exceptional families A.S.D. is inherited through an autosomal dominant gene of rather low penetrance (Campbell and Polani, 1961b), and there may be a few similar families with congenital aortic stenosis.

Familial cardiomyopathy is almost certainly a congenital malformation, though often it does not become manifest until adult life. It is an example of inheritance through a dominant autosomal gene with a higher degree of penetrance (Bishop *et al.*, 1962) of a condition described by Evans (1949) as familial cardiomegaly. The most remarkable example is the French-Canadian family starting in the seventeenth century that were described by Paré *et al.* (1961). An account of another syndrome of cardiomyopathy, multiple flat pigmented naevi, dwarfism, and electroencephalographic changes is shortly to be published by Polani and Moynihan (personal communication): this syndrome is transmitted dominantly, either by a single gene with pleiotropic effect or by two closely linked genes.

Medial necrosis of the aorta is often found with arachnodactyly (Marfan's syndrome), and rupture of the aorta is not uncommon as the mode of death, though the anomalies of the skeleton and the eye are perhaps better known. It is another condition that is inherited as a Mendelian autosomal dominant character. The mean excess of paternal over maternal age is in the same high range as in achondroplasia (eight years in the series of Lynas, 1958), and the sporadic cases are thought to be mutations caused, partly at least, by the high paternal age.

Recessive Mendelian Inheritance

This is of more general importance, and situs inversus is the best example of a malformation of the heart where it is the major cause. In 379 families (40 personal and 339 reported) of a propositus with complete (324) or partial (55) situs inversus the parents were first cousins in 20 or 5.3% (Campbell, 1963). This is more than 10 times the level expected in the general population of Britain. A recessive autosomal gene must play an important part in the aetiology of situs inversus, and often this is accompanied by other malformations.

It cannot be accepted as the complete explanation, because concordance between two monozygotic twins is not the rule (Campbell, 1963), though it is more common than concordance between twins with other malformations of the heart (see below). Further, in these 379 families there were 392 sibs with situs inversus (including the propositi) and 1,400 normal sibs, a proportion of 1 to 3.6. In recessive inheritance this proportion should, of course, be 1 to 3 ; but in the relatively small human families, which can only be ascertained when at least one sib is homozygous and therefore affected, so many normal children must be missed that the proportion is 1 to between 1.1 and 1.5. The proportion found is therefore very much lower than would be expected for a recessive gene with full expression. This and the lack of concordance show that environmental factors must be a partial cause, though recessive inheritance seems to be the main one.

There is some support for these views from *animal breeding experiments*. Tihen *et al.* (1948) found 57 mice with situs inversus among 227 offspring of inbreeding within a particular strain of laboratory mice. This was thought to be about half the number that would be expected for inheritance through an autosomal recessive gene with full expression. Baker-Cohen (1961) found situs inversus viscerum in 37% of an inbred line of the domesticated Fury strain of the platyfish (*Xiphophoris maculatus*), though it was rare or absent in most strains of this or related sword-tails. He too concluded that it was due to an autosomal gene or genes lacking full expression.

Apart from these two examples, there is similar evidence about *ventricular septal defect*. Although one of the more common malformations of the heart in mammals, Siller (1958) had seen very few examples in birds. In some strains of domestic fowls, however, he found 288 examples of V.S.D., and thought they had a genetic cause, because 97% of them were confined to three inbred lines, in which 84%, 50%, and 30% respectively were affected. Crossing experiments suggested some form of recessive inheritance. The defects looked quite like human V.S.D. and had the same haemodynamic and pathological effects.

There are few other cardiac malformations where genetic factors can with confidence be regarded as playing the predominant part, but many where the evidence points to them playing an important part.

Genetic Factors as a Partial Cause

1. First-cousin marriages in each of our groups of malformations, except coarctation of the aorta, are between two and three times as common as in the general population of Britain (mean incidence 1.1% against 0.4–0.5%). This is high enough to suggest that recessive inheritance plays some part in producing malformations of the heart. It could be an important part, because they are relatively common, and with a common gene one cannot expect to find such a high percentage of cousin marriages as with a rarer one.

2. The excess of mean paternal over mean maternal age in each of our separate groups (average, 3.27 years) is greater than that found in the general population (2.74 years). The difference was between 17% and 27% above the expected level in all our groups, except coarctation, where it was probably not significant (6%). Penrose (1955) thinks this is suggestive of a genetic cause, though the excess is not nearly as large as that found in Marfan's syndrome or achondroplasia.

3. A malformation of the heart was found in nearly 2% of the sibs of our propositi. This could be due to environmental influences in the uterus, but the high degree of concordance between the malformations in the propositus and the sib (60% the same and another 20% partially so) is more readily explained by genetic factors.

4. Monozygotic twins provide evidence for the importance of genetic as well as environmental factors. In three series containing 32 pairs of monozygotic twins (Uchida and Rowe, 1957 ; Lamy *et al.*, 1957 ; Campbell, 1961b), unselected except that one member of the pair was known to have a malformation of the heart, the second member of the pair was normal in every case (Table IV, Campbell, 1961b). This shows that concordance is unusual and that the malformation must be made manifest by an environmental cause. The most likely cause is some disturbance of the circulation of one of the twins because of the common placenta and chorion in more than half of them. Obviously twinning is of little numerical importance as a cause of malformation, but similar disturbances of the blood-supply to the foetus could be significant in other cases.

Nevertheless, some genetic predisposition is suggested by the many reported pairs where both members were concordant. Fuhrmann (1958) in 68 reported, and therefore selected, pairs of twins (excluding those in the three unselected series just mentioned) found 40% of the monozygotic pairs but only 25% of the dizygotic pairs were concordant for some cardiac malformation, most often of the same type (Table V, Campbell, 1961b). To add to the personal pairs reported in this paper, Dr. Arthur Hollman has given me particulars of monozygotic twin sisters who both had a successful operation at the age of 15 for an ostium secundum type of A.S.D.

Environmental Causes

Rubella

Rubella affecting the mother during the first trimester of pregnancy is the most clearly proved environmental

cause—perhaps the best-established of all causes—but not one that explains a large proportion of cases. The risk of abortion or of malformations is high, between 40% and 60% during the first four weeks, between 30% and 50% during the second four weeks, between 20% and 40% during the third four weeks, still perhaps a little during the fourth four weeks, but not increased later than this (Campbell, 1961a).

Deafness is the greatest risk, followed by malformations of the heart, and then cataract ; all may occur alone or quite often in combinations. Of the heart malformations P.D.A. is much the most common (58%), then come V.S.D. (18%), Fallot's tetralogy (7%), A.S.D. (6%), P.V.S. (6%), and all others (5%); in 6% of them all P.D.A. and V.S.D. were both present, and this is not a common combination under other circumstances. It is strange that a persistent ductus should be so common, since a patent ductus is normal long after the first trimester, when rubella produces its effects and becomes abnormal only when it *persists* for more than a few days after birth.

Numerically, maternal rubella is not a major cause of malformation of the heart. Three of the highest estimates are 4% (Conte *et al.*, 1945), up to 6% (Mouquin *et al.*, 1956), and 8% for one persistent ductus series (Keith *et al.*, 1958) ; but in larger series Gibson and Lewis (1952) found it to be 1.2%, Lamy *et al.* (1957) also 1.2%, and in my own experience 1.7% at the most. It seems fair to say that maternal rubella may be responsible for between 1% and 2% of all malformations of the heart.

The occurrence of abortions as well as malformations, the serious effects on the foetus with little risk to the mother, the characteristic pattern of the malformations, and the influence of the particular stage of the development—these are all features of the rubella syndrome and are four of the five generalizations laid down by Wilson (1960) about the action of teratogens in experimental animals. Even the fifth, that they often act in a complementary fashion to the genotype, may also be applicable, since malformations are produced only in a proportion of those exposed, and one of my own examples was the child of a first-cousin marriage.

Other Viral Infections

Other viral infections were naturally suspected as a cause when the significance of maternal rubella was realized, but there is not much evidence of their importance. In my series there are examples of malformations following maternal infections during pregnancy—by measles, chicken-pox, whooping-cough, herpes zoster, and infectious hepatitis—but only one or two instances of each. Other infections, such as mumps, poliomyelitis, influenza, and perhaps toxoplasmosis (Fraser, 1959), have been incriminated in isolated cases. After all the attention that has been paid to this subject in recent years it seems certain that no infection other than rubella is of the same importance as a cause, and it is unlikely that any of the others are responsible for a large number of malformations.

Though there is little evidence that ordinary vaccination against smallpox during pregnancy can produce malformations, I have seen one malformed heart following it, and MacArthur (1952) found that abortions and stillbirths were more common among mothers vaccinated between the fourth and twelfth weeks. In animals hog-cholera vaccines given to sows in early pregnancy have produced abortions and several malformations (but not of the heart), and similar results have been seen with blue-tongue virus in sheep (Rhodes, 1960).

Other Environmental Causes

In my series several malformations of the heart occurred after pregnancies in which there had been severe bleeding or threatened abortion or in which injections of corpus luteum or other preparations had been given to avoid a miscarriage. Lamy *et al.* (1957) also found a history of such episodes twice as often as in their control series.

Aminopterin, used as an abortive ; busulphan, used for therapeutic purposes (Warkany, 1960) ; and, more recently, thalidomide have all produced malformations in man as well as in animals ; but no drug has, so far, been incriminated as a cause of many malformations of the heart.

Deprivation of vitamins, and other abnormality in diets, can produce malformations of many types. Wilson and Warkany (1949) and Wilson *et al.* (1953) found that malformations of the aortic arches and the bulbus and defects of the ventricular septum occurred if mother rats were kept on diets deficient in vitamin A. The poor diet and malnutrition of many mothers a generation ago might have led to such malformations, but the vast improvement that has taken place in the former without any reduction in the incidence of malformations makes this most unlikely. It is possible that an unknown vitamin or some special amino-acid deficiency might be an important cause, but this is mere speculation.

Cox (1964) found that malformations in general (though not those of the heart) were twice as common in the children of mothers who had been exposed to frequent *x*-ray examinations for congenital dislocation of the hip.

Malformations Produced by Teratogens in Animals

A few examples of the interrelationship of genetic and environmental factors in experimental animals are given below. As long ago as 1927 Ford and Huxley showed that the degree of expression of the gene responsible for the melanin deposition in the eye of the gammarus depended on the temperature at which development took place. The interplay of these two factors has been emphasized particularly in the work of Landauer and of Warkany and their collaborators. They found that different strains reacted very differently to the same teratogenic agent ; that a particular malformation might be produced only in one or a few strains ; and that many malformations were apt to occur in a particular strain without any teratogenic agent, though then in a much smaller proportion of cases.

Landauer (1945, 1947) found that after injection of insulin into the yolks of eggs before incubation the percentage of rumpless chickens produced varied widely in different strains : this was also found if injections were given later, but then the malformations were in the bones of the leg and in the eyes. Landauer (1952, 1953) found large variations in the teratological effects of boric acid in different breeds of fowl and some variation in different mothers of the same breed: outcrossing Black Minorcas with White Leghorns produced a large fall from the previous incidence of defects.

Kalter (1954a, 1954b) showed that cortisone in suitable doses caused cleft palate in 100% of mice of strain A but in only 19% of strain B. When a female of strain A was crossed with a male of strain B, 43% were affected ; but when a male of strain A was crossed with a female of strain B only 4% were affected. This, he thought, showed the importance of the uterine environment also. Later, Kalter and Warkany (1957) found that the addition of galactoflavine to a diet deficient in riboflavine greatly increased the teratogenic effect, and the incidence of different malformations varied greatly in the different strains, and sometimes occurred only in one strain.

As further examples, Andersen (1949) producing vitamin-A deficiency, Ingalls *et al.* (1953) exposing animals to lack of oxygen, and Trasler (1958) injecting 4-amino-aspartic acid, all found different proportions of deformities in the offspring of different strains of pregnant mice.

Conclusions

Few malformations of the heart in man can at present be attributed to single genes or to other known genetic or environ-

mental factors acting alone: generally some genetic factor is effective only under certain environmental conditions. When starting, I should have regarded this as an unsatisfactory compromise, but it agrees with the conclusions of others, and much of the experimental work shows that the effect of many teratogens depends on the genetic constitution of the animals concerned.

Lamy *et al.* (1957) thought that the relative importance of these two causes varied in the different groups. If my figures are added to theirs (Tables I and III) they even out the difference to some extent, but genetic influences are still more important in pulmonary stenosis, and least important in coarctation of the aorta (excluding such causes as are found in Turner's syndrome), and after this in V.S.D. and Fallot's tetralogy. Larger numbers are needed to be sure of these differences, especially as pulmonary stenosis is at one end of the scale and Fallot's tetralogy near the other end, though these two are similar and not very uncommon in the same family.

Fuhrmann (1961, 1962) agrees that neither the constitution nor the environment, acting alone, can provide a satisfactory explanation. In his view the development of the heart is governed by a multifactorial genetic system with a balance of many interacting genes at different loci. Any change in the balance—for example, a rise in homozygosity—may cause a breakdown, so that exogenous factors, normally rendered harmless by the self-regulation, can lead to malformations. He thinks this view is in conformity with the genetic homoeostasis of Lerner (1954)—the tendency of a population as a whole to retain the genetic constitution arrived at by its evolutionary history, since natural selection favours a balanced system with a high incidence of heterozygosity to encourage the mean and at the same time to allow for variation and possible adaptation.

Neel (1960) reached very similar conclusions about many of the non-cardiac malformations in man: (1) children with multiple defects occur more often than can be explained by chance ; (2) with most defects there is an increased risk of their recurrence in subsequent sibs, generally in the same form ; (3) consanguineous marriages result in children with defects more often than other marriages ; (4) there is rather low concordance between monozygotic twins ; and (5) mothers with advancing parity and age, particularly those over 40, give birth to more children with defects. The first four are exactly, and the fifth is to a lesser degree, the same as our conclusions for malformations of the heart. There are, therefore, almost certainly similar causes. Neel too thinks they can be explained best on the hypothesis that defects are the phenodeviants resulting from complex multifactorial genetic systems with a positive adaptive value (as with sickle-cell anaemia)—the balanced polymorphic or homoeostatic systems of the type discussed particularly of Lerner (1954).

Foxon (1959) wrote : " A zygote will develop into a normal animal if its genetic constitution is normal, and if the environment in which development takes place is normal." I agree that either of these factors alone can cause malformations of the heart but think that more often both are at fault. If this is so, the genetic liability to malformations is not likely to be changed in the near future, but the environmental factors that make them manifest might be, when they have been discovered.

Need for Prospective Study

Retrospective studies cannot be relied upon to reveal these environmental factors. The mother who has given birth to a malformed child will search her memory for a possible cause, though I have been impressed by the number who refer to incidents in or near the second month of pregnancy when they are unlikely to know this is the critical period.

A prospective study on a large scale is therefore needed. Malformations in experimental animals have been produced in a great number of ways. Wilson (1959) lists 60 methods and divides them into six main groups. Though women are not likely to be exposed to such large doses of powerful chemicals or to such strict deprivations of essential nutrients, all these possibilities should be considered.

Full details about a large number of women during the first trimester of pregnancy, and even shortly before conception, should therefore be collected. Special attention should be paid to *any* deviations from the normal in diet ; to *any* infections, especially viral infections ; to *any* drugs given, however harmless they may be thought to be ; and to *any* injections, especially those used for avoiding (or producing) miscarriages. There seems a good chance that such an inquiry would be rewarding, and it might reveal something quite unexpected.

Although the large Collaborative Perinatal Research Project being carried out from Washington by the National Institute of Neurological Diseases and Blindness is concerned primarily with cerebral defects, I hope from what Dr. Lenore Bajda has kindly told me that it may cover also many of these aspects of malformations of the heart.

Summary

Our findings in the families of 1,227 patients with malformations of the heart are summarized and compared with those of others. The different forms must each be studied separately in the hope of finding more specific causes, but our main conclusions apply to malformations of the heart in general.

Simple genetic factors or exclusive environmental factors acting alone are not often the cause, though a few uncommon conditions show dominant Mendelian inheritance. In general, recessive inheritance is more important, but this genetic liability to malformation is made manifest only under certain environmental conditions. Some inbred strains of mice, fowl, and fishes have, however, shown a very high incidence of situs inversus or ventricular septal defect. These conclusions are in substantial agreement with those of Lamy *et al.* (1957) and of Furhmann (1962).

We agree with Furhmann that certain adverse environmental factors may normally be rendered harmless by the homoeostatic multifactorial genetic system responsible for the development of the heart, but that when there is some change in the balance of this system the same factors will produce a malformation. A large prospective study is needed to establish the more important environmental factors, in addition to maternal rubella, so that the number of malformations may be reduced.

Neel (1960) thinks this is the explanation also for many non-cardiac malformations in man. There is much experimental evidence that a malformation is often caused by a teratogenic agent in an animal genetically liable to that malformation.

I am grateful to Dr. Evan Bedford, Dr. Bonham Carter, and Dr. John Goodwin for helping with similar inquiries about their patients with A.S.D., P.D.A., and V.S.D. respectively, and the last-named for collaborating in the study of the V.S.D. series.

I should like to thank especially Professor P. E. Polani as co-author of some, and as a willing helper with many valuable suggestions in all, of this series of papers ; and Professor Foxon for his help with this last paper.

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Value of Ampicillin in the Hospital Treatment of Exacerbations of Chronic Bronchitis

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Authoritative teaching on the management of chronic bronchitis stresses the importance of giving antibacterial agents for acute exacerbations (Crofton, 1963 ; Garrod, Scadding, and Watson, 1963). But Johnston (1963) reviewed the clinical evidence of the nine controlled clinical trials of treatment of exacerbations of bronchitis which had been carried out up to that time and found that definite evidence of benefit was shown in only one trial. In his opinion the evidence in favour of the long-term prophylactic use of antibiotics was more definite than that in favour of the therapeutic use for acute illnesses.

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The pathogenic organisms which are considered important (May, 1958) are *Haemophilus influenzae* and *Streptococcus pneumoniae*. These are often found in the sputum during acute exacerbations, and the sputum usually becomes purulent (Elmes and White, 1953). There is histological evidence (Lynne Reid, 1958) that bacterial invasion during acute exacerbations causes the permanent damage to the lung. However, antibiotics given between exacerbations produce no immediate benefit even when the sputum is purulent, although the same " pathogenic " bacteria are often found in the sputum (Elmes, Knox, and Fletcher, 1953).

The routine use of antibiotics in the management of patients with acute exacerbations of bronchitis admitted to hospital gives