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Twins and Congenital Heart Disease

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The proportion of twins among total births remains relatively constant in most communities, though it varies in different countries and races. Thus it falls from 20 per thousand in same African negroes (Bulmer, 1960) to 14 per thousand in Norway, and to between 5 and 6 per thousand in Japan; and from 14.3 in the non-white population to 11.3 per thousand in the white population of the United States of America (Lilienfeld and Pasamanick, 1955). Further, the higher chance of twins in some families than in others is recognized widely enough for an increased premium to be demanded in these families to insure against such a possibility.

The different patterns of behaviour found between monozygotic and dizygotic twins are of great interest in the study of inheritance. The incidence of monozygotic twins is not known to be influenced by the environment, and even in countries like Japan where fewer twins are born, it is about the same as in Europe and America, 3,2 per 1000 (Penrose, 1959). One possible exception to this is that Lilienfeld and Pasamanick (1955) found fewer in the lower-income groups of white Americans, but they thought this might be explained by a higher abortion rate.

The incidence of dizygotic twins, on the other hand, is influenced by environmental as well as by genetic factors. Thus, it is only 2.0 per 1000 in Japan compared with 7.8 per 1000 in Europe (Penrose, 1959). Further, it becomes more frequent with advancing maternal age and incresasing birth order (Waterhouse, 1950, and McArthur, 1954) and less frequent with deficient nourishment. Thus, Bulmer (1959) has shown that the incidence of dizygotic twins, but not of monozygotic twins, decreased in those countries of Europe where undernourishment was common during the 1939-45, war, i,e., in Holland, Norway, and most of France, but not in Sweden or Denmark.

If two monozygotic twins always had the same congenital heart disease and dizygotic twins had not, it would be useful evidence for a genetic cause. Such pairs have been reported by a few authors, including myself (Campbell, 1944 and 1959), but much more frequently when one is affected, the other is normal (Uchida and Rowe, 1957; and Lamy, de Grouchy, and Schweisguth, 1957). This has been our experience also in a larger series of twins, but other points of interest have arisen: for example, there seems to be a higher incidence of congenital heart disease in monozygotic twins, but only in one member of the pair.

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In 1955, Polani and Campbell reported the number of twins in families where one child at least had congenital heart disease. A few were acyanotic and must now be excluded as they are included in the families of the propositi with one of the common forms of congenital heart disease that we are reporting here. Among the remaining cyanotic cases, mostly Fallot's tetralogy, there were 11 multiple maternities (10 twin and 1 triplet) and 831 children (306 propositi, 8 other affected sibs, and 517 normal sibs). In no case did both twins have congenital heart disease. In 6 pairs one was affected and one was normal, and in all these six pairs the twins were of the same sex. In the other 5 pairs none were known to be affected, though some who died in infancy may have been. Here, in contrast with the first group, only one pair were of the same sex, the other four being of opposite sexes. The numbers were small, but further experience confirms this difference.

Analysis of our Twins

We have now studied the families of 942 propositi with simple pulmonary stenosis (P. V. S), with ventricular septal defect (V. S. D) (unpublished data), with atrial septal defect (A. S. D) (Campbell and Polani, 1961b), with persistent ductus arteriosus (P. D. A) (Polani and Campbell, 1960), or with coarctation of the aorta (Campbell and Polani, 1961a) as well as the original group with Fallot's tetralogy. The patients were consecutive hospital and private patients, selected only in the sense that we chose those with the cammon malformations and with the diagnosis proved by catherization or operation or necropsy in the great majority. In all, there were 38 multiple maternities (37 twins and 1 triplet) in the 942 families with 2801 children. This is little more than might be expected by chance (see later).

Sex Incidence. These pairs of twins (Tables I and II) are not, however, evenly distributed as regards their sex, as should be the case. Where one member of the pair was affected and the other was normal, 14 pairs were of the same sex and only 2 of opposite sexes. In 15 of these 16 pairs, the affected twin was the propositus with the malformation shown in the first column: the sixteenth pair (A129) were sibs of a propositus with atrial septal defect and the living boy was normal but the other boy had died when 19 days old with some congenital heart disease, the nature of which is not known though A. S. D is likely because of the frequency with which two affected sibs both have the same heart malformation (Campbell and Polani, 1961b).

Where, on the other hand, both members of the pair were normal, 7 pairs were of the same sex and 8 of opposite sexes — a striking contrast with those where one of the pair was affected.

Where the condition of one or both was unknown (7 pairs), there were 5 pairs where one was affected and the other died young, so that both may have been affected. It seems probable that this was so in at least one, for the twin girl died when she was 2 with pneumonia after whooping cough, and at this age the atrial spetal defect had not yet been diagnosed in her cotwin who survived (114). The three other twins of the same sex died at 12 days (PS119) or at 12 hours (C41) or were stillborn (PS5).

The fifth, a twin boy of the girl with a ventricular septal defect, died at 36 hours (V190). In these last four we have no evidence whether the second twin who died had heart disease or not. Of these 5 pairs, 4 were of the same sex and only 1 of opposite sexes. In the remaining 2 pairs, we do not know about the presence or absence of heart disease in any of the four, for there were a pair of twin boys and a pair of twin girls, all of whom were premature and died in infancy, in families where the propositi had P. D. A.

There were, therefore, 27 pairs of the same sex and 11 sets (10 pairs and 1 set of triplets) of opposite sex. Among dizygotic twins there should be equal numbers of the same and of opposite sexes and the addition of the monozygotic twins, who generally make up 25 to 30 per cent of the total, must increase the proportion of the same sex. Assuming 28 per cent are monozygotic, one would expect 64 (28 + half 72) per cent of like sex and 36 (half 72) per cent of unlike sexes, or in our 38 sets, 24.3 and 13.7 pairs. The 27 and 11 pairs found show a small excess of pairs of the same sex.

The excess of pairs of like sex was entirely due to the 21 pairs where one at least had congenital heart disease (Table I). In these 21 pairs, there were 18 of like sex, instead of the expected 13.4 and only 3 of unlike sex instead of the expected 7.6 pairs. The high proportion (86 per cent) of the same sex could hardly occur unless there were unusually high proportion of monozygotic twins among those with congenital heart disease. In the 15 pairs where both were normal, 7 were of like sex (expected 9.6) and 8 were of unlike sex (expected 5.4).

Some details of these twin pairs, excluding the 15 where both members of the pair were normal, are given in Table II, including the age of the mother when the twins were born, and the zygosity and birth weight of the twins where these were known. Information about zygosity is very incomplete, but the mean age of the mothers of twins of like sex was 28.4 years and of mothers of twins of unlike sexes 33.1 years, in accord with the observation that the birth of dizygotic twins, but not of mo-

Table 1. Incidence of Twins with Congenital Heart Disease and Normal Twins in our Families

Heart lesion	No. of families	No. of children	No. of pairs of twins	One affected One normal		Both normal		One affected one unknown		Total	
				same sex	opposite sex	same sex	opposite sex	same sex	opposite sex	same sex	opp. sex
Fallot's tetralogy	306	831	11	6_0	0	1	4_0	0	0	7	4
P. V. S.	125	407	7	1	1	1	2	2	0	4	3
V. S. D.	111	338	4	2	0	0	1	0	1	2	2
A. S. D.	170	543	4	2	0	0	1	1	0	3	1
P. D. A.	123	323	7	1	1	3	0	2_0	0	6	1
Coarctation	107	359	5	2_0	0	2	0	1	0	5	0
Total	942	2801	38	14	2	7	8	6	1	27	11

Table 2. Some Details of the 23 Twin Pairs where One was Affected (or Unknown in two)

Reference No.	Maternal age at birth	Affected twin			Other twin
		Sex and age	Birth weight (lb.)	Cong. malf.	Sex, condition, and (where known) zygosity and birth weight
(1) One affected and one normal: (a) of same sex (14)					
0253	39	M. 33	4.2	Fallot's t.	M. Normal ? 3.8 lb.
0140	41	F. 22	—	Fallot's t.	F. Normal MZ —
0079	28	M. 20	—	Fallot's t.	M. Normal MZ —
0037	35	F. 10	—	Fallot's t.	F. Normal ? —
0193	29	F. 16	—	Fallot's t.	F. Normal ?DZ —
0237	21	M. 24	—	Cyanotic H. D.	M. Normal MZ —
PS33	34	F. 46	3.2	P. V. S.	F. Normal ?DZ 3.0 lb.
V14	30	M. 15	6.0	V. S. D.	M. Normal ?DZ 6.5 lb.
V15	29	F. 46	—	V. S. D.	F. Normal ? —
A70	27	F. 28	4.7	A. S. D.	F. Normal ? 6.6 lb.
A129	26	M. 2	5.0	?A. S. D.	M. Normal ? 5.2 lb.
G51	22	F. 14	5.6	P. D. A.	F. Normal ? 5.6 lb.
C99	23	F. 18	7.0	Coarct.	F. Normal MZ 6.5 lb.
C77	29	M. 22	5.7	Coarct.	M. Normal ? 5.4 lb.
(b) of opposite sex (2)					
PS39	24	F. 24	4.5	P. V. S.	M. Normal DZ 4.5 lb.
G12	39	F. 27	7.0	P. D. A.	M. Normal DZ 7.0 lb.
(2) One affected and one unknown (a) of same sex (4)					
PS5	23	F. 11	6.4	P. V. S.	F. Stillborn ? —
PS119	—	F. 10	—	P. V. S.	F. Died at 12 days ?MZ —
A114	24	F. 26	5.5	A. S. D.	F. Died, aged 2 yr. ? 6.5 lb.
C41	23	M. 10	4.2	Coarct.	M. Died after 12 hr. ? 4.0 lb.
(b) of opposite sex (1)					
V82	28	F. 12	3.9	V. S. D.	M. Died at 36 hr. DZ 4.0 lb.
(3) Both unknown and of same sex (2). In each case, the propositus, a sib of the pair, had P. D. A.					
G76	23	Both girls and premature (2.8 & 3.0 lb.) and both died in 48 hrs.			
G117	21	Both boys and premature and both died at 3 weeks.			

nozygotic twins, increases with increasing maternal age (Waterhouse, 1950). There did not seem to be any reason for including the pairs of twins where both were normal in Table II: they were born in the families of the propositi with congenital heart disease and were distributed as shown in Table I.

Monozygotic and Dizygotic Twins

Unfortunately our information about zygosity is very incomplete. This is partly because in routine clinical work with congenital heart disease, especially when it is cyanotic, its effects on the size and appearance of the twin with this may mask the close similarity that makes one suspect the twins are identical. Four of these pairs of twins, three in the Fallot group and one with coarctation, have been fully investigated by Evans (not yet published) and all were shown to be monozygotic pairs, so that he too wondered if monozygosity did not in some way increase the risk of congenital heart disease.

Certain deductions can, however, be made if the numbers are large enough for statistical treatment, for then the dizygotic pairs must include equal numbers of pairs of like and of unlike sex. Thus, if the number of pairs of unlike sex is U and the number of like sex is L, there would be 2 U dizygotic pairs and L — U monozygotic pairs (Weinberg, 1909). Among our 36 pairs (omitting the 2 where the cardiac status is not known) 25 are of like, and 11 of unlike sex; and so 22 would be dizygotic and 14 monozygotic. For the smaller numbers in our subdivisions, the error of this method would be greater: roughly, however, where one twin was affected and the other normal or unknown, 15 of the 21 would be monozygotic instead of the 6 calculated from the expected sex incidence of twins; and where both were normal, all or nearly all 15 pairs would be dizygotic.

This suggests that the mere fact of being a monozygotic twin makes the presence of congenital heart disease in one, but only in one, of the twins much more likely.

The Expected Incidence of Twins

The number of children in our families should allow us to make a reasonably accurate estimate of the number of twins to be expected if these behaved in the usual way. We have found that malformations of the heart are not influenced by maternal age, so there should be no undue excess in our families of older mothers who are more liable to have dizygotic twins. Our finding of 38 twin maternities among 2801 children is a little, but not significantly, more than the 34 or 35 twin pairs that would be expected from the figures of 12.2 per thousand for 1938-48 and 12.5 per thousand for 1955 given by the Registrar General.

Twin maternities form about 1 in 80 (12.5 per 1000) of all maternities but the number of twins born, 1 in 41.7, is rather less than twice this, because the still-birth rate is 53 instead of 23 per 1000 (Registrar General, 1955: 8437 twin maternities in a total of 675,026). The mortality of twins is also greater, especially in the neonatal period:

Sandon (1957) estimated that 85, instead of 95, per cent were living after ten years, but we have made no allowance for this as we think we have included most of those who died young. Among these 2801 children we might, therefore, expect to find 67.2 twins, 33.6 pairs, but there were 38 which is rather more, but not significantly so.

In the community of 2801 children, 942 were propositi with congenital heart disease (C. H. D) — 1 in 2.97. We might therefore expect the same proportion of our 67.2 twins. i.e., 22.6, to have C. H. D.: this would be 22.6 pairs where one was affected and the other normal, leaving 11 pairs where both were normal. The number found was 21 (16 from columns 5 and 6 of Table 1, and 5 from columns 9 and 10), but there were 9 children in the twin pairs where we do not know if they had C. H. D or not because of their early deaths. Suppose 3, the expected proportion, of these 9 had C. H. D., the final number, 21 + 3, would be a little above the expected number, as the total number of twins was.

It may seem surprising that there was no pair of twins where both were affected, but this is not so. The general incidence of C. H. D is no more than 6 per 1000, so for the 44.6 (67.2 — 22.6) other twins, only 0,27 might be expected to have C. H. D and one could not expect to find a twin pair with both affected unless one was dealing with a much larger sample. If, as seems more accurate, we calculate the figure on the higher incidence of 2 per cent that we have found in the sibs of our propositi, one would expect it to be 0.89: we have, therefore, accepted the expectation of 1 pair where both were affected, and reduced the expected number where one was affected and accepted the expectation of 1 pair where both were affected, and reduced the expected number where one was affected and the other normal to 21.6 pairs (see Table III).

Assuming there were the usual proportion of monozygotic twins (28 per cent) one would expect the 22.6 affected pairs to be divided into 14.5 pairs of like sex and 8.1 of unlike sex, or 6.3 monozygotic and 16.3 dizygotic pairs. In fact, we found 18 instead of 14.5 of like sex and 3 instead of 8.1 of unlike sec. We calculated that 15 (instead of 6.3) were monozygotic and 6 (instead of 16.3) were dizygotic. This different, but not completely independant, approach to the problem confirms our view that one of a pair of monozygotic twins is more likely to have congenital heart di-

Table 3. Expected and Observed Incidence of Normal and Affected Twins, and of Mono- and Di-zygotic Twins

No. of pairs	Total		Of like sex		Of unlike sex		Monozygotic		Dizygotic	
	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Calc.	Obs.	Calc.
Both twins affected	1									
One twin affected	21.6	21	14.5	18	8.1	3	6.3	15	16.3	6
Both twins normal	11	15	7.0	7	4.0	8	3.1	0	7.9	15
Both twins unknown	0	2	—	2	—	0	—	—	—	—
Total	33.6	38	21.5	27	12.1	11	9.4	15	24.2	21

sease than would be expected by chance. Correspondingly the dizygotic twins showed some deficiency of affected twins and some excess of pairs where both were normal.

Discussion

The Proportion of Monozygotic Twins with Congenital Heart Disease. We have found reasonably close agreement between the observed and expected number of all twins with congenital disease. Polani and Campbell (1955) concluded that there was no obvious association between the incidence of twinning and the incidence of congenital heart disease ($X = 0.03$ in their Table 14) and the present enquiry supports this, though there is a small excess of all twins in these families. Lamy et al. (1957) also found no difference in the proportion of twins among their propositi with C.H.D and among their controls. The series of Uchida and Rowe (1957) does not help us since their twins were selected to include only those pairs where one had a cardiac malformation, and this applies still more to individual case reports.

Looft (1931) in Norway pointed out that there was an increased incidence of twins among mental defectives. Recently, Berg and Kirman (1960) found twice as many twins among their mental defectives as among the general population, and this seemed to apply to monozygotic and dizygotic twins equally, though concordance as regards the defect is more common among the former.

When, however, we consider the monozygotic and dizygotic twins with congenital malformations of the heart separately, there is some evidence that these are more likely to occur among monozygotic twins. In our series 15, instead of the expected 6.3, were thought to be monozygotic and 6, instead of the expected 16.3, dizygotic. The lower incidence of dizygotic twins is difficult to explain without assuming a higher pre-natal mortality for them: if this is so, the higher mortality would presumably apply to the monozygotic twins also and would make their original increase over the expected number still larger.

Most other reported cases of twins with congenital heart disease do not help us in this because we do not know about the numbers or status of the other members of the family. Lamy et al. (1957), however, gave details about all the twins where the propositus was one of the pair. Where one (or both) of the twins were affected nearly half (7 of 16) were monozygotic, and generally these should form only about one quarter of the total. The series of Uchida and Rowe (1957) adds some further evidence that monozygotic twins are more liable to have malformations of the heart than dizygotic twins are, since they made up half of the total number instead of the usual quarter. But 19 of their original 45 pairs were omitted because information was not complete and these may have included more dizygotic twins.

There is, therefore, some evidence that monozygotic twins are more likely to suffer from malformations of the heart than dizygotic twins or the other sibs, though it is not yet as complete as could be wished.

Concordance or Discordance in Monozygotic Twins. Many examples of concordance between a pair of twins have been reported, and generally the pair has been monozygotic. Among our 38 pairs of both types, however, there was no pair where both were known to be affected, though there were 16 where one was affected and one normal, and 7 where one was affected and one unknown. In the series of Lamy et al. (1957) both twins were affected (both with pulmonary valve stenosis) in one pair, a dizygotic pair of twins; in the other 8 dizygotic pairs and in all the 7 monozygotic pairs, one twin was affected and the other was normal; but they do not give any information about the normal pairs in their families with congenital heart disease. In the series of Uchida and Rowe (1957) where the pairs were chosen because one twin was affected, the other was normal in each of the pairs, of which 13 were monozygotic and 13 were dizygotic pairs.

The results in these three series are shown in Table IV. In 58 pairs, 32 were thought to be monozygotic and only 26 dizygotic. All the excess of the former is due to my series where the chance of zygosity was calculated from the sex distribution of the pairs, but even without these, the high proportion of nearly half the cases where one twin (and one twin only) was affected were monozygotic pairs.

Among these 32 pairs of monozygotic twins where one had congenital heart disease, there was no example where the second also had C. H. D. This is conclusive evidence that concordance is unusual, and that most C. H. D. cannot be due entirely to genetic causes. This will be discussed later.

Other Personal and Reported Cases. It seems worth a short discussion of these other cases, though they cannot help us much, since we do not know whether they were reported mainly because they were monozygotic or because both members had con-

Table 4. Concordant and Discordant Malformations in Series of Twins Unselected except that One at least had C. D. H.

	Uchida & Rowe (1957)		Lamy et al. (1957)		Campbell (1961)		Total	
	Conc.	Disc.	Conc.	Disc.	Conc.	Disc.	Conc.	Disc.
Monozygotic	0	13	0	7	0	12	0	32
Dizygotic	0	13	1	8	0	4	1	25
Total	0	26	1	15	0	16*	1	57

* In the other 5 pairs, one was affected and the other died young without us knowing whether the heart was affected or not.

genital heart disease. There is some evidence that both these reasons influence the likelyhood that the case will be reported and this is what might be expected. Thus I have notes of eight other pairs of probable monozygotic twins, where the propositus

has a malformation of the heart, the other twin having the same malformation in three pairs, being normal in three pairs, and dying young with the condition of the heart uncertain in the remaining two pairs. During the same period I have not collected any similar notes about dizygotic twins, but I may have seen some, especially where only one was affected, and failed to keep any record of this. These eight pairs have been excluded from the earlier part of the paper because I do not know the total number of cases from which they were selected or the number of sibs in their families, so that they are of no use for statistical purposes.

The first pair of sisters were reported during the War (Campbell, 1944) and the addresses were lost then so I have not been able to see them again: in retrospect, there seems no doubt that they were monozygotic twins, but some doubt about the diagnosis of a small ventricular septal defect thought not about the presence of some minor malformation of the heart.

The second pair of sisters both had a persistent ductus but I saw only one member of the pair ten years after her ductus had been closed successfully: I had no doubt from what her mother said that she and her sister, who had died in 1942 from haemorrhage at her operation for a persistent ductus were monozygotic twins, nor had Shallard (1945) any doubt about this when he reported them as Cases II and X.

Besterman (personal communication) has given me details about a pair of monozygotic twin brothers, both of whom had recently undergone successful surgical treatment for Fallot's tetralogy.

A girl, aged 13, had the general features of Fallot's tetralogy but there were some reasons for thinking that she had pulmonary atresia. Her monozygotic twin sister was normal.

A girl, aged 4, had pulmonary atresia with a continuous murmur from a persistent ductus or a large bronchial artery. Her sister was normal and was thought to be a monozygotic twin though this was not certain.

A girl, aged 12, had characteristic signs of a moderate-sized ventricular septal defect and has got on well with few symptoms for another five years. Her monozygotic twin sister was said to have the same condition but I thought her systolic murmur was functional. [1]

A boy had a successful valvotomy for simple pulmonary stenosis when he was 5 and has got on well for another 7 years. He was one of a pair of monozygotic twins with a single placenta and the circulation of the two twins communicated freely. The second twin was born dead and there was no information about the condition of his heart.

A woman with Fallot's tetralogy, who died at the age 54 with congestive heart failure, was said to be one of a pair of identical twins, the other having died in infancy;

[1] Since this were written Dauchas has seen a similar pair of twin girls aged 5 months, who were thought to be identical twins. Both were said to have congenital beart disease but Dauchas thought that one had a ventricular septal defect and the other an innocent murmur: both, however, had been born with a hare-lip.

but after this length of time it was not possible to find out if the death was due to congenital heart disease or not.

The most complete collection of reported cases I know is that of Fuhrmann (1958). His results, omitting the series of Polani and Campbell (1955), of Uchida and Rowe (1957), and of Lamy et al. (1957) because they are already in our Table IV, are shown in Table V, to which I have added the 6 personal cases just reported, where I could say if the pair were concordant or discordant. There were 56 pairs that were monozygotic and only 12 that were dizygotic. Clearly this shows they were selected and

Table V. Concordance and Discordance in Reported Twins where One at least had C. D. H.

Twins	Complete situs inversus		All other C. D. H.		Total	
	Conc.	Disc.	Conc.	Disc.	Conc.	Disc.
Monozygotic	6	4	16	30	22	34
Dizygotic	1	0	2	9	3	9
All	7	5	18	39	25	43

These are taken from the cases reported by Fuhrmann (1958). The series of Polani and Campbell (1955), Uchida and Rowe (1957), and Lamy et al. (1957) have, however, been excluded here as they are included in our Table IV, but six personal cases, not in our general series, have been added.

not representative cases and throws doubt on other conclusions that might be drawn from them.

Even so, one was affected and one was normal in 43 of the 68 pairs and the proportion was greater, but not enormously greater, in the monozygotic than in the dizygotic twins. The cases of situs inversus have been listed separately because this is the condition that is most certainly inherited as a Mendelian recessive character (Cockayne, 1938) and here the concordance betwen monozygotic twins was more common but by no means universal.

The 22 pairs of concordant monozygotic twins are, of course, of great interest, but they are less significant than the fact that none were found in the three series shown in Table IV. Possibly, they also add a little support for the view that malformations of the heart are more common in monozygotic twins, and at least they are not against this view.

Genetic or Environmental Causes. Many examples of all sorts of diseases have been reported in both members of a pair of monozygotic twins, and the subject has been dealt with fully by Gedda (1951). In same conditions there is a high degree of concordance, and at the other extreme there are conditions like congenital malformation of the heart where it is unusual.

Our Table V includes 16 pairs of monozygotic twins with the same malformation of the heart, as well as the 6 others where both had situs inversus, so clearly this is not extremely rare. Certainly, however, the three series of consecutive cases, selected only because a malformation was present in one member of the pair (Table IV) show that this is exceptional rather than the rule; and that much more frequently, when one is affected, the other is normal The cause cannot, therefore, be purely genetic, but the occurrence of concordant pairs suggests a genetic predisposition that becomes manifest only under certain conditions of the environment.

It is not unreasonable to suggest that both genetic and environmental factors can be involved. Foxon (1959), reviewing the experimental work on malformations of the heart, emphasized that normal development depended on a normal genetic constitution *and* a reasonably normal environment; and that under certain conditions the same malformation could be produced by genetic *or* environmental causes *or* by the appropriate combination of these two factors. If, as our evidence suggests, one of the pair of monozygotic twins is affected more often than would be expected by chance, this is another reason for thinking that environmental causes must be the most important, or at any rate the most direct, factors involved.

In monozygotic (MZ) twins, a higher proportion are known to have a single placenta. Stern (1960) quotes a table from Steiner (Arch. Gynak., 159., 1936) showing that 70 per cent of MZ twins but only 44 per cent of DZ twins have a single placenta; and, even more significant, that 57 per cent of MZ twins but no DZ twins have a single chorion. Unfortunately, this information is less often available to the cardiologist. This difference often provides a less perfect circulation for the two MZ foetuses, and it may be deficient in one and conversely excessive in the other of the individual members of the pair. This can be compared with the findings where one of a pair of MZ twins has acardia or hemi-acardia and depends for its circulation on the heart of the normal twin, a condition that may be found also in some conjoined twins (Willis, 1958).

Gedda (personal communication) has suggested that the malformation of the heart may be caused by lack of oxygen determined by this irregular functioning of the maternal-foetal circulation due to the type of placentation, and that this is the explanation of the higher proportion of monozygotic twins affected by cardiac malformations. Polani (personal communication) has suggested that the increased blood flow could equally well be the cause of some cardiovascular malformations. This suggestion accepts that haemodynamic forces are of great importance in normal development of the heart and great vessels and considers that, when these deviate from normality, cardiovascular malformations may result. In twins such deviations may result from vascular communications between the two twins, which for the reasons given are much more likely in MZ twins. This suggestion receives support from the work of Bremer (1932) who brought forward evidence of the importance of the blood flow on the development of the heart. Either of these alternatives of an increased or a decreased blood flow could be the important factor, and the latter could act indirectly by allowing an inadequate supply of some substance such as vitamin A, which Wilson, Roth, and Warkany (1953) found was capable of producing malformations in rats.

Summary and Conclusions

The number of twins in 942 families where the propositus had a congenital malformation of the heart has been studied. The 38 pairs were not significantly more than could be expected by chance: nor were the 21 pairs where one member had a malformation of the heart. In 16 pairs, one was affected and the other normal; and in 5 pairs, one was affected and the other unknown. In 2 pairs, both were unknown because of early deaths; and in 15, both members of the pair were normal. In no pair were both members known to be affected.

There is clear evidence from this series and from the series of Uchida and Rowe (1957) and of Lamy et al. (1957) that where one member of a pair of *monozygotic* twins has a congenital malformation of the heart, the other is generally normal. It is the exception rather than the rule for both members to be affected, though several examples of such pairs have been reported.

There is some evidence from these three series that monozygotic twins are more liable to have a malformation of the heart than dizygotic twins and their sibs.

It follows from these two findings, that the immediate cause of the malformation of the heart must be environmental, though probably there is some genetic predisposition. A disturbance of the foetal circulation to the affected twin because of a single placenta and chorion seems to be the most likely environmental cause.

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RIASSUNTO

Sono state studiate le coppie gemellari facenti parte di 942 famiglie di affetti da malformazione cardiaca congenita. Le risultanti 38 coppie non erano in numero molto più alto di quanto ci si sarebbe potuto attendere; nè lo erano le 21 coppie nelle quali un membro presentava una malformazione cardiaca. In 16 coppie un membro era affetto e l'altro normale, in 5 coppie un membro era affetto e l'altro sconosciuto; in due coppie le condizioni di ambedue i gemelli non erano note a causa di morte precoce; in 15 coppie ambedue i membri erano normali. In nessuna coppia i due membri risultavano ambedue affetti.

Da questa serie e dalla serie di Uchida e Rowe (1957) e di Lamy et al. (1957) risulta che quando un membro di una coppia di gemelli monozigotici presenta una malformazione cardiaca congenita, il cogemello, generalmente, è normale. Il caso di ambedue i gemelli affetti costituisce l'eccezione piuttosto che la regola, benchè siano stati riportati numerosi esempi di coppie concordanti.

Da queste tre serie appare anche che i gemelli monozigotici sono più suscettibili di presentare malformazioni cardiache di quanto non lo siano i gemelli dizigotici e gli altri membri della loro fratria.

Da questi reperti risulta che la causa immediata della malformazione cardiaca deve essere ambientale, benchè vi sia, probabilmente, una certa predisposizione genetica. La causa ambientale più probabile sembra essere costituita da un disturbo della circolazione fetale, nel gemello affetto, causato dal fatto che la placenta ed il corion sono unici.

Desidero ringraziare il Prof. Gedda di Roma ed il Prof. Polani per i loro utili suggerimenti, ed il Dr. I. E. Evans per avermi lasciato osservare il suo lavoro non ancora pubblicato sull'evidenza di monozigotismo in alcune coppie gemellari incluse in questo lavoro.

RÉSUMÉ

Sur 942 familles, le nombre de jumeaux ayant une malformation du cœur ont été étudiés; 38 couples ne signifiaient pas plus que ce qu'on pourranit attendre du hasard; pas plus que les 21 couples où un membre avait une malformation du cœur; chez 16 couples, l'un était atteint et l'autre normal; chez 5 couples, l'un était atteint et l'autre inconnu. Pour 2 couples, tous les deux étaient inconnus à cause de mort précoce; et pour 15, les deux membres du couple étaient normaux. Chez aucun couple l'on ne trouva tous les deux membres atteints.

Il est évident, d'après cette série, ainsi que de celles d'Uchida et Rowe (1957) et de Lamy (1957) que là où un membre d'un couple de jumeaux monozygotiques a une malformation congenitale du cœur, l'autre est généralement normal. C'est l'exception plutôt que la règle, que les deux jumeaux soient atteints, bien que plusieurs exemples de tels couples aient été relevés.

En étudiant ces trois séries, on trouve la même évidence: les jumeaux monozygotiques sont plus sujets des jumeaux dizygotiques aux malformations du cœur.

Il s'ensuit de ces deux découvertes que les causes immédiates de la malformation du cœur proviennent du milieu, quoi qu'il existe probablement des prédispositions congénitales. Un trouble circulatoire dans le fœtus, qui sera le jumeau affecté, causé par le fait d'un seul placenta et un seul chorion, sera très vraisemblablement la cause exogène de la malformation.

Je voudrais remercier le Professeur Gedda, de Rome, ainsi que le Professeur Polani pour leurs utiles suggestions; et le Docteur I. E. Evans pour m'avoir laissé voir son travail, non publié, sur l'évidence pour le monozygotisme dans quelques couples de jumeaux inclus dans cet article.