A Family Study of Fallot's Tetralogy

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This analysis concerns Fallot's tetralogy, a form of cyanotic congenital heart disease about which there is little information relating to the population of north east England, and attempts to assess the influence of familial and other variables possibly concerned in its aetiology. This disease of the heart is named after Fallot who described it in 1888, though it had been recognized as a clinical entity over 200 years previously (Stensen, 1671). Classically, the condition includes 4 features: pulmonary obstruction, ventricular septal defect, right ventricular hypertrophy, and dextroposition of the aorta. Physiologically the combination of a ventricular septal defect with an obstruction of the pulmonary outflow tract results in a predominantly right to left shunt. The degree of overriding of the aorta varies individually, but it is the size of the ventricular septal defect together with the degree of pulmonary obstruction which determines the severity and clinical picture. The classification of congenital heart disease in childhood produced by the International Society of Cardiology (Watson, 1970) recognizes this by including the tetralogy in the category 'ventricular septal defect with obstruction of the right ventricular outflow tract'.

Method and Material

The survey covers the families of 100 index patients, each of whom could be regarded as conforming to the classical concept of Fallot's tetralogy. These consisted of 22 patients from Newcastle General Hospital whose average age was 13 years and 78 from the Royal Victoria Infirmary, Newcastle, whose average age was 7 years. Of these, 50% and 71% respectively were born in hospital. For each *propositus*, an attempt was made with the family doctor to obtain a control matched for age, sex, social status, and area of residence, and so far 47 control families have agreed to cooperate. From all these families, both of *propositi* and control children, family data were obtained, physical examination of the nearest relatives was carried out whenever possible, and histories of relatives of remoter degree examined. Any relative suspected of having a congenital heart condition

was followed up through his hospital record, death certificate, or family doctor in order to ascertain the type of heart defect, if any. Each mother was also asked about her health before and during the pregnancy with particular emphasis on the first trimester. Besides these 100 *propositi*, there were a further 12 who were omitted. Four families declined to cooperate, 3 were omitted where there were special reasons (recent death of the mother or psychological difficulties), 2 where the child was diagnosed as having Down's syndrome, and 3 where it was clear that the tetralogy was part of some other identifiable syndrome (Treacher-Collins, Marfan, Klippel-Feil). The last 5 families were excluded in an endeavour to make the series as homogeneous as possible.

Figure 1 shows the age at which the clinical diagnosis of congenital heart disease was made. Despite the difference in age and in the proportion of *propositi* born in hospital between the two series, the distribution of ages at diagnosis is very similar indeed. The majority of cases are found in the first 3 months when the presenting symptoms are usually failure to thrive, feeding difficulties, and respiratory infections. Some indeed may be suspected in the neonatal period, for 30% are reported by the mother as having looked blue at birth and half of these had breathing difficulties. A second group is discovered through the cyanotic attacks that usually occur later when the child becomes more active, and these lead to diagnosis usually at about 1 year of age. Two *propositi* in the survey, both mild cases, were not diagnosed until they were 2 and 3 years old; the former only became cyanosed when he began to run about, the latter when he developed measles. In all these cases the diagnosis was confirmed by cardiac catheterization, surgery, or at necropsy.

The index patients fell into two groups. The majority (group I) showed no other cardiovascular anomaly besides the tetralogy, and these clinically appeared to range in severity (Table I) at the time of survey or previous surgery from the deeply cyanosed to the mildly affected. Severity is of course not absolute since there is a tendency for some to worsen the longer surgery is deferred. A minority of *propositi* (group II) showed pulmonary stenosis and ventricular septal defect together with some other cardiac or cardiovascular anomaly. In 4 there was an atrial septal defect. In 3 the left pulmonary artery was absent, as described by Nadas *et al* (1953), and in 2 there was anomalous systemic venous drainage. Cases of ventricular septal defect with pulmonary atresia were not included in this series.

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FIG. 1. Age at diagnosis of congenital heart disease.

TABLE I
CARDIAC MALFORMATION IN INDEX PATIENTS

	Male	Female	Total
<i>Group I</i> Pulmonary outflow obstruction and ventricular septal defect			
Severe	29	10	39
Moderate	25	21	46
Mild	2	4	6
<i>Group II</i> Pulmonary outflow obstruction and ventricular septal defect and other cardiac or cardiovascular anomaly	4	5	9
Total	60	40	100

The sex distribution of the propiiti showed a pronounced male preponderance, a sex ratio of 1.5. There appear to be differences in the sex distribution according to the degree of severity of the defect, the male preponderance being most noticeable in the most severe cases, but this does not attain statistical significance.

One of the propiiti was a member of a pair of dizygotic twins, his co-twin being unaffected. Only one propiitus was the offspring of a detectably consanguineous union between 2nd cousins.

The propiiti tended to be of low birth weight. For affected males the mean weight (lb) was 7.18 ± 0.17 , by comparison with their normal male sibs (mean $7.50 \pm$

0.12) and with the control series (mean 7.43 ± 0.21). For females the figures are respectively 6.95 ± 0.18 , 7.45 ± 0.11 , and 7.39 ± 0.22 . Gestational age has to be taken into account, and when this is done the difference between adjusted means is significant at 5% in females but is not significant in males.

Results

Environmental Factors

The family environment. Table II shows the maternal age at birth of the propiitus and, for comparison, the expected numbers in each maternal age group as compared with the Registrar General's figures (1960) and those in the control series. The difference from the Registrar General's figures is not significant. By comparison with the control series there appears to be an excess in the younger maternal ages, but this is due to a departure of the control series from the Registrar General's maternal age distribution. The mean maternal age at the birth of the propiiti was 26.29 ± 0.62 with a standard deviation of 6.20, while the mother's age at birth of the control children was 28.42 ± 0.95 with a standard deviation of 6.55 years. Similarly there is no significant difference from the paternal ages at

TABLE II
MATERNAL AGE AT BIRTH OF PROPOSITUS

	Age (yr)						
	< 20	20-24	25-29	30-34	35-39	40 +	
<i>Groups I and II</i> Number observed	8	34	35	12	6	5	$\chi^2 = 4.56$ (NS)
Number expected	6.26	30.77	30.45	19.23	13.12		
Controls	2	14	11	13	7	—	

TABLE III
PATERNAL AGE AT BIRTH OF PROPOSITUS

	Age (yr)						
	< 20	20-24	25-29	30-34	35-39	40 +	
<i>Groups I and II</i> Number observed	2	21	31	26	10	8	$\chi^2 = 1.73$ (NS)
Number expected	3.06	19.83	31.26	24.56	22.2		
Controls	1	12	10	14	10	—	

TABLE IV
PARITY

Age of Mother at Birth of Propositus	Number of Previous Live Born Children							
	0	1	2	3	4	5	6	7
15-19	5	1						
20-24	21	9	4	1				
25-29	7	12	6	5	0	1		
30-34	1	7	4	2	1	1		
35-39	0	2	1	3	0	0		
40-44	2	0	0	1	0	1	1	
45-49	1	0	0	0	0	0	0	
Mothers of propositi Number observed	37	31	15	12	1	3	1	
Number expected	37.3	30.6	16.2	12.7	3.8	2.0	1.1	1.3
Mothers of controls Number observed	19	10	12	2	1	3	0	

birth of the control children (Table III). The mean paternal age at the birth of the propositi was 30.20 ± 0.69 with a standard deviation of 6.83 years, and for the control series the mean was 30.19 ± 0.98 with a standard deviation of 6.72.

The parity of the mothers is set out in Table IV where the numbers are compared with those expected from the Registrar General's figures for the northern region with which there is very close correspondence. By comparison with the control series, however, there is an excess of propositi born in the 2nd and 4th pregnancies, and a deficit in the 3rd pregnancy. There is obviously no consistent pattern here. The results of the 220 pregnancies of the mothers of propositi, excluding those pregnancies that produced the index patients, are given

in Table V. Of these 220 pregnancies, there resulted 28 abortions (12.7%) a proportion similar to the 15% estimated by Warburton and Fraser (1964). The cause of one stillbirth at 8 months was unknown, though the mother attributed it to the shock of the sudden death of her own mother. The 2nd stillbirth resulted in an anencephalic child and the 3rd was the product of an obstructed labour due to malpresentation, the dead child being delivered by Caesarean section. The miscarriage rate is similar in the control series. While there is general similarity in the outcome of the pregnancies before and after the affected child more pregnancies took place before that resulting in the propositus than afterwards. This suggests either that affected children tend to occur in later pregnancies, or that

TABLE V
RESULTS OF PREGNANCIES IN THE MOTHERS OF INDEX PATIENTS

Sex of Proband	No. of Stillbirths	No. of Abortions	No. of Unaffected Sibs		No. of Affected Sibs	
			Male	Female	Male	Female
<i>Male</i>						
Born before proband	1	14	30	33	0	2
Born after proband	1	5	24	17	0	1
<i>Female</i>						
Born before proband	1	7	25	27	0	0
Born after proband	0	2	19	10	0	1
Total pregnancies excluding propositi (220)	3	28	98	87	0	4
<i>Half sibs</i>						
Born before proband	0	0	3	5	0	0
Born after proband	0	0	0	0	0	0
Total pregnancies (8)	0	0	3	5	0	0
<i>Controls</i>						
Total pregnancies (117)	0	18	46	53	0	0

the birth of an affected child limits the subsequent family building. The former is excluded by consideration of the parities in Table IV above.

There appears to be no effect of season of birth of propositi, the numbers in each quarter (January–March, April–June, etc) being respectively 23, 27, 29, and 21. The slight excess in the 3rd quarter is not statistically significant. Analysis by social class as indicated by the father's occupation (Table VI) shows the distribution to be very similar to that given by the Registrar General (1960), the majority of births occurring in families of social class group III. Thirty-two per cent of the patients' mothers worked outside the home, usually in shops, offices, and factories, during early pregnancy compared with 27% of the control mothers. Three of the former were hospital nurses and therefore more likely to be in contact with infections.

Maternal health. The general health of mothers in the two groups was very similar. Three mothers of propositi thought that they had been in contact with german measles and had developed a rash at 6, 8, and 10 weeks of pregnancy, but the

diagnosis was not confirmed at the time and none of the 3 index cases showed other stigmata of the rubella syndrome. Other infections during the first 3 months which were specifically mentioned were influenza, frequent colds, herpes simplex, and gastroenteritis; 13 mothers in the affected group had experienced one of these infections (13%) compared with only 9% in the control group. Contact with other childhood infections (measles, mumps, chicken pox) was enquired into, but was reported in neither group. There was only one diabetic mother of an index patient and one 'control' mother was found to be a diabetic after producing two healthy sons. The latter also had thyrotoxicosis and subsequently underwent surgery for this condition after the birth of the second baby. One mother in the study group had had a thyroidectomy before she became pregnant and was permanently taking Eltroxin, she was also given a course of Butazoladin during the first trimester for thrombophlebitis of the leg. Another mother was thought to have myxoedema after the birth of the index patient, but she had received no treatment for this condition. One other mother had thrombo-

TABLE VI
SOCIAL CLASS OF INDEX FAMILIES

	Social Class*					Separated
	I	II	III	IV	V	
<i>Groups I and II</i>						
Number observed	1	12	48	21	12	6
Number expected	14.43		47.48	22.04	10.05	—
Controls	—	8	21	11	7	0

* Registrar General's groupings (1960).

phlebitis but received no medical treatment for the condition (apart from rest in bed).

Five mothers in each group had been treated for anaemia before becoming pregnant and during pregnancy 86% of the study group took iron tablets compared with 53% of the control group. Active tuberculosis had occurred and been successfully treated in 3 study-group mothers and 2 control mothers before pregnancy. In each group there were a few bronchitics whose cough was aggravated by heavy smoking. The proportion of women who smoked was similar in each group; 27 in the study group of whom 8 smoked heavily (more than 15 cigarettes daily) and 19 in the control group with 4 heavy smokers. There was one epileptic mother of an index patient who was treated continuously with Epanutin and Phenobarbitone. Alimentary disease did not occur in any of the mothers seen, but urinary infections were mentioned by 8 study group mothers and one control mother.

As regards health during the first trimester, vaginal bleeding was experienced by 20 mothers at some time during the first trimester, a few reported a slight loss lasting one day but 6 needed bed rest and 2 required drugs to prevent aborting. This is in marked contrast to the control group where only one mother reported slight bleeding when 3 months pregnant. The numbers in each group who had pregnancy vomiting were similar but 21% experienced moderate or severe sickness in the affected group compared with 10% in the control group. Five mothers of index patients and 7 mothers of controls had received a chest x-ray early in pregnancy.

The drugs taken during the first trimester were many and varied, particularly in the mothers of propositi. Drugs prescribed by family doctors were not usually known by name and in many cases on direct enquiry to the general practitioner the information was not available. Slightly more control mothers took anti-emetic tablets in proportion compared with the affected group. Antibiotics and sedatives were prescribed for 5 mothers in the study group, and for only one mother in the control group. Stilboestrol was given to one mother with a threatened abortion and a 2nd mother, who was 45 years of age, was taking the same drug for menopausal symptoms. When she stopped taking it (because she had suspected signs of early pregnancy) she experienced vaginal bleeding. Another mother had had 'hormone' treatment to prevent a possible early abortion following 2 previous miscarriages. Self medication was more difficult to assess but 15% of the study group had taken aspirin for headaches and minor illnesses compared with 9% of the control group. One had taken Trihexin slimming tablets

early in pregnancy and another mother admitted buying tablets for 'cramp'. Thus drugs other than anti-emetics were prescribed for 9 mothers of propositi but 2 of controls, and were self administered by 18 and 4 respectively.

Family History. There is a striking tendency for congenital cardiac lesions to occur in other members of these families, ascertained by the occurrence of a child with Fallot's tetralogy. Figure 2 shows two families in which at least 2 members were affected, but it is obvious that there is no simple Mendelian pattern. This tendency to familial aggregation is well demonstrated in Table VII, showing the number of families with at least 1 other relative affected with congenital heart disease. Out of the 100 families of the Fallot propositi 8 showed some relative with Fallot's tetralogy and 16 showed some relative with other congenital heart disease. By contrast out of the 47 control families, in only 3 is there a relative with congenital heart disease and none with the tetralogy.

TABLE VII
NUMBER OF FAMILIES WITH AT LEAST ONE
AFFECTED RELATIVE

	Fallot's Group	Control Group
Number with congenital heart defect	23*	3
Number with tetralogy of Fallot	8	0
Total number of families	100	47

* One child had 2 affected relatives.

Examining these relatives more closely (Table VIII and Appendices 1 and 2), out of a total of 189 live born sibs of the propositi, there were 4 affected with congenital heart disease; 3 were sisters of male propositi, and one the sister of a female proposita. In this last family the child died of a lesion identical to that of her sister. In another family the infant died soon after birth, she had been recognized as being a 'blue baby' but there was no necropsy and 'congenital heart disease' was stated as the cause of death. The sister of the 3rd boy was recognized as having a continuous cardiac murmur which was suspected to be due to a peripheral pulmonary branch stenosis. She died suddenly from acute pneumonia; the necropsy showed a small patent ductus arteriosus and right ventricular hypertrophy, but unfortunately peripheral pulmonary branch stenosis was not specifically sought and the diagnosis was therefore unconfirmed. The sister in the 4th family had a ventricular septal defect which did not require operation. In addition to these 4 sibs, a

FIG. 2a. Family tree of C.T. (III.7). The maternal grandfather (I.7) had talipes of the left foot. The father (II.4) aged 33 was known to have had a heart murmur as a child; he was not cooperative and refused to be examined or x-rayed. A brother (III.5) died at 1½ years of congenital atresia of the bile ducts. A sister (III.8) died at 3 years of pneumonia; she was known to have congenital heart disease and necropsy showed an enlarged heart, right ventricular hypertrophy, and patent ductus arteriosus.

FIG. 2b. Family tree of P.P. (III.8). A maternal cousin (II.11) died in 1960 at 6 months; he had multiple defects including a cleft palate and Fallot's tetralogy. His sister (II.12) was stillborn and his brother (II.13) died at 2 days of a virus infection. A second cousin (III.1) of the proband died in 1965 of tricus arteriosus and a ventricular septal defect.

TABLE VIII
NUMBER OF AFFECTED RELATIVES BY DEGREE OF RELATIONSHIP

Degree of Relationship	Fallot's Tetralogy					Controls	
	No. of Relatives	No. Affected	No. Concordant	No. Partially Concordant	No. Discordant	No. of Relatives	No. Affected
1st (sibs)	189	4	2	1	1	90	0
2nd	1165	2	1	1	0	429	0
3rd	2531	4	2	2	0	1124	3
4th	Many	6	3	1	2	—	—
5th	Many	8	0	4	4	—	—

further 3 were found to have had benign heart murmurs as children, but these had disappeared spontaneously and all 3 were normal when examined and all were regarded as such in this analysis. In the 99 sibs of control children, none had any cardiac lesion. Of the parents of the probandi, the father of one of the families with 2 affected children was known to have had a heart murmur as a child, when seen he looked cyanosed, but he refused examination or other diagnostic measures. Another father was also known to have had a heart murmur as a child, but had served in the Navy and was found to be normal on examination. None of the mothers was found to

have any heart defect. Only 2 of the index patients were married, and each had produced a normal child. As regards more distant relatives, 1165 second-degree relatives of the probandi were traced, of whom 2 were found to have had some congenital heart defect. For one the death certificate was non-informative but from his history it seems that he was probably concordant (ie, a Fallot's tetralogy); the 2nd was partially concordant (a ventricular septal defect). There were no affected second-degree relatives out of the 429 traced in the control series. There were also 2531 third-degree relatives of the probandi who

were traced, and 4 were found to be affected; one was concordant, one probably so (Fallot's tetralogy), and 2 were partially concordant (ventricular septal defect). In the control series there were 3 affected cases out of 1124 traced. Other cases of congenital heart disease have been found in more remote relatives of the *propositi*, though it is not possible to give the data in incidence form since at this distance of relationship bias is very likely to enter into the reporting; one is more likely to remember the existence of a second cousin with the same lesion as one's own child. However, of the 6 affected fourth-degree relatives the lesion was discordant in 2, and of the 8 affected fifth-degree relatives, it was discordant in 4. It seems that the more distant the relationship to the index patients, the less likely is the lesion to be identical; this is compatible with the findings of Davison (1967). At this distance of relationship the incidence is probably approaching that of the general population.

Associated Malformations. There is a high incidence of associated non-cardiac malformations in the *propositi* (Table IX), even though the definitive

TABLE IX
NON-CARDIAC MALFORMATIONS IN INDEX
PATIENTS BY SEX

Index Number	Malformation
<i>Males</i>	
5	Cleft lip and palate
47	Cleft lip
11	Hiatus hernia
28	Congenital cataract
24	Webbing of neck
15	Hypoplastic left kidney
8	Undescended testicle
18	Hypospadias
51	Ptosis of left eye; bossing of forehead; curious facies
23	Severe mental retardation
<i>Females</i>	
92	Hydronephrosis
79	Deformity of right arm and hand
84	Bilateral talipes, odd facies, absent nails on little finger and several toes
87	Talipes of right foot
98	Cleft palate
97	Severe mental retardation

syndromes have been excluded. Among skeletal abnormalities, one boy had a cleft lip and palate, another boy a cleft lip, and one girl a cleft palate. In one girl the right ulna was absent and she had only one right finger and thumb. One girl had talipes valgus of the right foot, another had bilateral talipes in association with absent nails on the left little finger and on several toes, and a curious facies. Among genitourinary abnormalities, there was one boy with a hypoplastic left kidney, one with an undescended testicle, and one with hypospadias.

There was one girl with a right hydronephrosis. Minor abnormalities included one hiatus hernia, one shortening of the neck (the chromosomes were normal), one boy with congenital cataract (non-rubella). Severe mental retardation was apparent in 2 children and 3 more were educationally subnormal. Three children were left with a hemiparesis following a cyanotic attack, a direct result of the heart condition, and in addition 2 children had idiopathic epilepsy, not associated with the heart condition. Altogether 16 children had some type of defect other than cardiac (excluding the 3 children with hemiparesis and the 2 with epilepsy).

This high incidence does not occur in their sibs. Of the 185 liveborn sibs, excluding the 4 with congenital heart disorders, one had died from congenital atresia of the bile ducts, and 7 had died from some other cause (2 from cerebral haemorrhage, one from a respiratory distress syndrome, 2 from pneumonia, one of septicaemia, and one of leukaemia); and there were 3 surviving with other disorders (one pyloric stenosis, one rib deformity, one large naevus). In the sibs of the *propositi* therefore the proportion of congenital defects compares favourably with the 2.6% observed by Williamson (1969) and 2.5% by McKeown and Record (1960). In the 99 sibs in the control group, the proportion of anomalies is rather higher. One with haemangioma of the liver had died; there were one each with exomphalos, severe kyphoscoliosis, talipes, spina bifida, undescended testicle, inguinal hernia, and coeliac disease; 4 sisters had xeroderma, and one child was epileptic. Thus the sibs of the *propositi* compare favourably with those of the controls, and though there is a high incidence of non-cardiac malformations in the *propositi*, this does not occur in their sibs.

Discussion

Family studies such as these of congenital heart defects pose many difficulties. Not all lesions can be detected at birth but are found at a later followup examination; babies may die at home without correct diagnosis of the condition. There is indeed a death rate of about 40% in the first 5 years of life so that only about 2.8 per 1000 survive to reach school age (Hay, 1966). Cardiovascular anomalies may account for half the deaths in the first year of life due to congenital defects (Mooring, 1966) and in Newcastle upon Tyne 10% of the children who died in hospital from all causes between 1960 and 1966 were suffering from some form of congenital heart disease (Roberts, Chavez, and Court, 1970). The present survey is therefore a sample survey, in which there may be some bias in that some children

born with the tetralogy of Fallot died before they could be incorporated in the survey or indeed diagnosed. However in view of the distribution of age at diagnosis, undiagnosed but surviving cases are not likely to be many. In other words the results are possibly biased towards the exclusion of the more severe and towards the inclusion of the less severe.

It is difficulties of this type that hinder the accurate determination of the incidence in the population of congenital heart disease. The frequency of congenital heart disease of all types has been variously reported as 3.2 per 1000 live births in Birmingham (McMahon, McKeown, and Record, 1953), 6.8 in Rochester, USA (Harris and Steinberg, 1954), 6.5 in Gothenburg, Sweden (Carlgen, 1959), and 4.7 in Liverpool (Hay, 1966). An overall figure of 6 per 1000 live births is usually adopted. Equally difficult is the identification of the population frequency of the different types of congenital heart disease. However figures are now emerging from the Newcastle Maternity Survey 1960-62, under the direction of Dr G. A. Neligan, who has kindly made the material available to us. In this period there was a total of 14,027 births excluding stillbirths and perinatal deaths (deaths during the first week). One hundred and thirty-three children were referred to a cardiologist with suspected congenital heart disease but a proportion of these proved to be clinically insignificant. Thirty-six children died before reaching school age and among this number were 3 with Fallot's tetralogy. In addition there were 5 more patients with Fallot's tetralogy who were included in our survey. On the reasonable assumption that no cases of Fallot's tetralogy died during the first week after birth, this gives a total of 8 cases of Fallot's tetralogy in 14,027 births which is very close to the estimate of 6 in 10,000 used by other workers. Such estimates derived from epidemiological data are of critical importance when attempting to estimate the genetic contribution to liability to develop particular types of heart disease.

Numerous cases of more than one family member being affected by congenital heart disease have appeared in the literature (Pitt, 1962; Holmes, 1965; Lynch, Tips, and Krush, 1966; *British Medical Journal*, 1967) and the tendency to familial concentration demonstrated (McKeown, MacMahon, and Parsons, 1953; Campbell, 1959; Nora and Meyer, 1966; Jackson, 1968). As a result, recent years have seen the emergence of several family studies, conducted to investigate the hereditary basis of different types of heart defect, persistent ductus arteriosus (Polani and Campbell, 1960), coarctation of the aorta (Campbell and Polani,

1961a), atrial septal defect (Campbell and Polani, 1961b; Nora, McNamara, and Fraser, 1967; Williamson, 1969), ventricular septal defect (Campbell and Goodwin, 1965), congenital aortic stenosis (Zoethout, Bonham Carter, and Carter, 1964), and atrioventricular defects (Emanuel *et al*, 1968). The aggregation that these family studies show is repeated in the present report. This shows that empirically there is, in sibs of a child with Fallot's tetralogy, a recurrence risk of Fallot's tetralogy of 1%, or of any type of congenital heart disease of 2%. In other studies the recurrence rate in sibs of propositi with congenital heart defect varies from 1% to over 3% according to the type of the defect. The recurrence rate for atrial septal defect of 3.6% and 3.7% found by Nora *et al* (1967) and Williamson (1969) respectively is one of the highest. The present figure of 2% recurrence rate of congenital heart defect generally amongst sibs is in broad agreement with the findings of Polani and Campbell (1955).

Our data are not yet sufficient to derive a reliable estimate of the hereditary component of Fallot's tetralogy, or indeed of concordant defects, or of congenital heart disease in general as ascertained by our present series. For example the frequency of congenital heart disease in second- and third-degree relatives of our propositi is below the population average. However from comparison of incidences here observed with those in the general population (Newcastle Maternity Survey) an estimate of the heritability of liability to Fallot's tetralogy may be attempted. The figure derived from sibs (ignoring the association with sex) is moderately high, $53.9\% \pm 16$. This is rather lower than the heritability of $69\% \pm 9$ for liability to atrial septal defect calculated by Williamson (1969). Such 'heritabilities' calculated from first-degree relatives alone may well be overestimates of the true additive genetic component of variance, and indeed the figure is slightly lower when sibs and relatives of second and third degree are pooled ($45.4\% \pm 14$). These figures must be accepted with caution until the reliability of the estimates from the more distant relatives can be improved. However from them reassurance can with certainty be given to patients who have survived to reproductive age, to the many more now able to do so as a result of surgical procedures, and to other members of families in which affected individuals occur, for from these figures the maximum expected proportion of second-degree relatives affected is approximately 1 in 370 and of third-degree relatives one in 780.

In this study, as in others (Campbell, 1965; Shaw, 1965; Feldt *et al*, 1968) it has been difficult to

identify environmental factors. Maternal age, parity, and social class were not significantly different from the general population. The slight increase in the number of births in the third quarter which might have indicated viral infections in the mother during the first trimester also proved not to be significant. Other authors however have reported some seasonal variation, Miettinen, Reiner, and Nadas (1970) a seasonal increase in coarctation of the aorta in the winter halfyear, Landtman (1965) finding an increase of children with atrial septal defect born in the late summer/early autumn, but though Williamson's highest quarterly total (1969) occurred in October to December of children born with atrial septal defect, the variation was not significant. There is obviously scope here for further enquiry.

The only variables, of all those examined in this survey, other than family history, to show some significant association concern maternal health. An increased proportion of mothers of propositi experienced vaginal bleeding during the first trimester; an increased proportion experienced moderate or severe hyperemesis; an increased proportion took drugs other than anti-emetics both by prescription and by self-medication. Such data from retrospective surveys are notoriously unreliable, but they are at least suggestive and point to the type of variable that should be considered in a prospective enquiry.

Of particular interest are 2 mothers who could well have taken abortifacients, of whom one was unmarried at the time of conception; indeed of the 37 primiparous mothers of propositi 10 had conceived antenuptially (by comparison with 2 out of 17 controls) and a proportion of these might have taken abortifacient drugs without admitting it. There is a growing literature on the association between drugs administered during pregnancy and specific congenital abnormalities in the fetus (Smithells, 1966; Burns, 1969; Nelson and Forfar, 1971) and there has been definite implication of drugs, eg, thalidomide, in Fallot's tetralogy and ventricular septal defect (Pliess, 1962). Thalidomide was of course not administered to the mothers of any of the subjects in the present survey, but the example shows that other drug involvement is worth consideration. The involvement of virus infection in the development of Fallot's tetralogy has been established for example in relation to cytomegalovirus infection (Lé Tan Vinh *et al*, 1956) and rubella (Desmond *et al*, 1970), and again though there is barely a suggestion in the findings of the present survey the point is worth further investigation. As a third pointer for further study, the slimming tablets taken by one mother may have

caused impairment of appetite and inadequate nutrition, while the hyperemesis suffered by so many may perhaps have interfered with nutrition of the fetus at a critical time of organogenesis (Foxon, 1959; Brent, 1969), particularly if the mother was able to retain little or no food, though in general the fetus is remarkably well buffered against nutritional inadequacy.

In conclusion then while this study has shown an inherited tendency to develop Fallot's tetralogy, represented by a positive fairly high heritability which accounts for about one half of the variation in liability to develop the condition, there is still ample scope for the operation of environmental factors. These may affect not only the development of the condition, but also its severity which has been shown to be variable, and perhaps the development of associated noncardiac malformations which occur at high frequency in the propositi but not in their sibs. The environmental variables that may be involved, including virus infection, drug susceptibility, and specific nutritional inadequacies have not been demonstrated in the present survey though their action is suspected in some cases.

Summary

The families of 100 patients with Fallot's tetralogy and 47 controls for age, sex, and social status were studied to assess the influence of genetic and environmental variables in the aetiology.

A tendency to familial aggregation of the condition and of other congenital heart defects compatible with multifactorial inheritance was discerned. Recurrence risk for sibs is 1% for Fallot's tetralogy and 2% for any form of congenital heart defect. The heritability of Fallot's tetralogy is estimated at 54%. The tendency for other noncardiac defects to occur in the patients with Fallot's tetralogy does not appear in their sibs.

Of the several environmental variables examined, only those concerning maternal health showed any possible association, threatened abortion and vaginal bleeding, infection in pregnancy, medication; these require investigation in a prospective survey.

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Appendix I

Initials and Index No.	Month and Year of Birth	Maternal Age	Paternal Age	Male Sibs (year of birth)	Female Sibs (year of birth)	Half-sibs (date of birth or no. of offspring)		Other Affected Relatives	Notes
						Male	Female		
Group I Male Index Patients									
One child family									
I.R.	1	7.64	24	26					
L.S.	2	7.58	22	21					
P.B.	3	10.68	28	32					
S.S.	4	1.66	22	23					
D.B.	5	8.68	19	28					
G.H.	6	8.65	24	24					
T.O'N.	7	7.65	45	33					
N.E.	8	10.58	45	61					
						3F's 1st wife 2M's 1st husband	1F's 1st wife 1M's 1st husband	Uncle: CHD*. Half brother's daughter: CHD*, ? FT	* Died 1920. * Died 1955.
J.L.	9	3.66	43	41					
C.H.	10	1.62	23	27					
S.P.	11	1.70	20	22					
R.H.	12	4.62	21	30					
D.L.	13	1.54	23	25					
Two child family									
R.O.	14	10.63	26	34	'66				
C.B.	15	8.65	27	24	'62				
A.W.	16	7.61	22	29	'59			2nd cousin: PDA or AV fistula	
S.W.	17	5.63	29	30	'47				
I.T.	18	9.63	31	38	'66			Father's 1st cousin: FT and pulmonary hypoplasia.	
G.B.	19	3.65	25	26		'63		Father's uncle: CHD*	* Died aged 17 (1922)
R.K.	20	8.63	27	32	'61				
J.W.	21	12.58	23	27	'54				
B.A.	22	6.61	32	33	'58				
T.D.	23	8.48	27	27	'44*				* Died at birth ? cause
P.P.	24	2.70	25	28		'67		Mother's 1st cousin: FT + ASD + cl. pal.	
							'62	Father's 1st cousin once removed: Tr. Art. and VSD	
J.M.	25	5.65	19	23	'68			Mother's mother's sister's daughter: PDA	
D.A.	26	7.66	25	37		'62			
T.S.	27	7.41	26	39	'48				
K.D.	28	10.53	33	39		'49			
M.McL.	29	6.62	22	24	'67			Father's mother's 1/2-sister's daughter: ASD and pulmonary atresia.	
								2nd cousin: VSD	
B.K.	30	6.56	27	37	'49				
Three child family									
J.N.	31	4.58	21	25	'62				
P.S.	32	2.59	26	31	'50				
R.A.	33	10.65	25	28	'53				
B.C.	34	11.58	20	23	'63, '67				
P.R.	35	4.65	20	22	'61				
					'64*				
					'67				
								Father's aunt: died valv. disease of the heart, aged 19: ? congenital or acquired	* Died hyaline membrane disease
K.McG.	36	5.60	29	32	'61				
T.K.	37	5.49	25	31	'67	'56			
					'45				

† For explanation of symbols (†) see the appropriate comment in the same line under 'Notes'.

Key to Appendices I and II

ASD = atrial septal defect; AV fistula = atrioventricular fistula; BSM = benign systolic murmur; C = concordant; cl. pal = cleft palate; coarct. aorta = coarctation of the aorta; CHD = congenital heart disease; D = discordant; FT = Fallot's tetralogy; HM = heart murmur; Prob. C = probably concordant; PC = partially concordant; PDA = patent ductus arteriosus; SB = still birth; T = twins; Tr. Art. = truncus arteriosus; VSD = ventricular septal defect.

Initials and Index No.	Month and Year of Birth	Maternal Age	Paternal Age	Male Sibs (year of birth)	Female Sibs (year of birth)	Half-sibs (date of birth or no. of offspring)		Other Affected Relatives	Notes		
						Male	Female				
Four child family											
M.B. 38	6.57	23	25	'65	'55, '56	'42, '45, '53	'46, '47	1st cousin once removed: FT	* Died 16 wk : asphyxia and miasma, * Died 8 wk: CHD ? FT		
N.D. 39	4.62	31	53	'59	'57, '65						
M.H.T. 40	4.60	35	37	'45, '49	'60 (T)						
S.R. 41	7.55	30	30	'53	'57, '58						
S.C. 42	3.69	25	28	'64, '66*	'63						
M.C. 43	4.64	22	24	'61, '65	'62*						
M.W. 44	10.62	31	38		'53, '57, '58						
C.F. 45	11.61	38	39	'46	'49, '58						
D.M. 46	6.69	41	43		'51, '52, '57						
K.McA.47	4.59	23	25	'57*	'63, '68						* Operated: pyloric stenosis
D.S. 48	6.64	29	30	'61, '67, '69							
M.R. 49	8.55	24	27	'62	'64*, '68				* Died 12 wk: pneumonia		
A.H. 50	2.68	31	32	'59, '61, '70							
Five child family											
C.T. 51	12.62	24	25	'60*, '61	'59, '64†			F. cyanotic and HM: refused examination	* Died congenital atresia of bile ducts. † Died 3 yr: ? PDA		
C.B. 52	8.62	24	24		'59*, '61, '64, '68				* SB.		
Seven child family											
P.W. 53	3.51	28	31	'40, '49, '55	'41, '44, '45*				* Large naevus removed		
P.C. 54	5.61	39	41	'55, '62, '63*	'46, '49, '53†, '58				* SB. † VSD		
P.C. 55	7.57	42	45	'47, '49(T), '52	'38, '41, '49(T)						
Eight child family											
A.G. 56	12.55	22	24	'51, '53, '58, '62, '64, '66	'59						
Group II Male Index Patients											
Two child family											
M.McC.57	12.63	24	26		'65			2nd cousin: coarct. aorta			
W.R. 58	4.63	24	30		'65						
Three child family											
M.M. 59	2.53	25	27	'58, '66				2nd cousin: VSD			
J.B. 60	4.61	24	28	'65, '68							
Group I Female Index Patients											
One child family											
J.H. 61	3.68	18	?					Mother's sister: VSD			
J.W. 62	3.66	19	20								
E.S. 63	3.68	20	22								
L.K. 64	3.52	23	25								
M.C. 65	5.61	29	32								
K.F. 66	3.48	29	30								
Two child family											
S.C. 67	7.57	24	25		'59			2nd cousin: ASD	* Since adopted		
B.J. 68	6.63	22	24	'67							
D.R. 69	1.65	31	33		'58						
J.McG. 70	8.56	24	22	'54							
S.G. 71	10.68	19	21		'67						
D.O. 72	7.64	25	25		'60						
W.N. 73	9.63	18	28	'65							
J.B. 74	11.60	26	32		'56						
K.T. 75	9.68	17	17	'70		'66*					
E.McL. 76	6.51	33	34	'40							
M.A. 77	8.62	36	41		'50						
M.A. 78	11.55	22	26		'59						
Three child family											
M.R. 79	8.68	28	31	'64, '65				1st cousin: died VSD 1st cousin once removed: PDA	* BSM as a child		
S.W. 80	6.61	23	24	'59, '65							
M.B. 81	12.57	22	26	'60	'54						
S.P. 82	1.64	29	33		'57, '58*						
M.B. 83	12.65	16	19	'67	'70						
M.W. 84	1.66	27	27	'64	'63						
C.B. 85	2.47	22	25		'45, '60	'58					
G.L. 86	11.61	25	25		'55, '57						

Initials and Index No.	Month and Year of Birth	Maternal Age	Paternal Age	Male Sibs (year of birth)	Female Sibs (year of birth)	Half-sibs (date of birth or no. of offspring)		Other Affected Relatives	Notes
						Male	Female		
<i>Four child family</i>									
D.McG.87	9.67	26	24	'62, '65	'64		'47	* Father's $\frac{1}{2}$ -sister's daughter's son VSD	* BSM as a child
J.D. 88	12.54	30	?	'48 (T), '52	'48 (T)				
S.C. 89	5.52	38	39		'37, '39, '46				
S.W. 90	11.66	29	35	'60, '61, '64					
L.G. 91	3.54	39	43	'49	'46, '47*				
<i>Five child family</i>									
J.M. 92	3.64	29	26	'58*, '60, '65, '69	'63				* SB
<i>Six child family</i>									
K.T. 93	7.60	27	30	'63, '66, '68	'58, '62				* Sister, died 5 yr: FT. † BSM
E.B. 94	10.59	20	21	'63, '69	'61*, '62, '64†				
<i>Seven child family</i>									
A.F. 95	9.59	31	32	'51, '53, '54, '57, '58, '64				Mother's 1st cousin died 1933: CHD, aged 13	
Group II Female Index Patients									
<i>Three child family</i>									
L.I. 96	8.65	25	28	'60*	'62				* Died leukaemia
J.K. 97	8.59	29	31	'55, '62					
<i>Four child family</i>									
C.H. 98	5.64	29	31		'59, '62, '69			Mother's sister's son: VSD	
<i>Five child family</i>									
K.E. 99	6.61	27	28	'57, '59, '67	'52				
<i>Eight child family</i>									
M.C. 100	9.55	31	31	'51, '57, '60, '63	'52, '53, '66				

Appendix II

Affected Relatives

Index No.	1st degree	2nd degree	3rd degree	4th degree	5th degree
<i>Males</i>					
T.O'N. 7		Father's brother: CHD, died 1920 (Prob. C)			
N.E. 8			$\frac{1}{2}$ -brother's daughter: FT (C)		
A.W. 16					Mother's mother's sister's son's son: PDA or AV fistula (D)
G.B. 19				Father's father's sister's daughter: died FT (C)	
R.K. 20			Father's uncle died: CHD, (1922) aged 17 (Prob. C)		
P.P. 24				Mother's mother's brother's son FT + Cl palate (C)	Father's mother's sister's daughter's son: Tr. Art. and VSD (PC)
D.A. 26				Mother's mother's sister's daughter PDA (D)	
M.McL. 29					Mother's father's $\frac{1}{2}$ -sister's daughter: died ASD and pulmonary atresia (D)
B.K. 30					Mother's father's sister's daughter's daughter: VSD (PC)
M.C. 43	Sister: died CHD, ? FT (Prob. C)				
K.McA. 47				Mother's sister's daughter's son: FT (C)	

Index No.	1st degree	2nd degree	3rd degree	4th degree	5th degree
C.T. 51	Sister: died ? PDA (D)				
P.C. 54	Sister: VSD (PC)				
W.R. 58					Father's father's sister's son's son: coarctation (D)
J.B. 60					Father's father's brother's daughter's son: VSD (PC)
<i>Females</i>					
J.H. 61		Mother's sister: VSD (PC)			
B.J. 68					Mother's mother's son's daughter's daughter: ASD (D)
M.R. 79			Father's sister's daughter: died VSD (PC)		
S.W. 80				Father's father's brother's son: PDA (D)	
S.W. 90					Father's 1/2-sister's daughter's son: VSD (PC)
E.B. 94	Sister: died FT (C)				
A.F. 95				Mother's mother's sister's daughter: CHD, died 13 yrs (Prob. C)	
C.H. 98			Mother's sister's son: VSD (PC)		