Genetic and Non-genetic Factors in the Etiology of Congenital Heart Disease: a Study of 1188 Cases

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INTRODUCTION

IN 1888, FALLOT described the anatomical defects of the heart in "blue babies;" his name has since been associated with the "ensemble of defects, manifold but constant," which characterize these infants. However, as early as 1777, a Dutch surgeon named Sandifort described the tetralogy now bearing Fallot's name (see Kuyjer, 1954). A century earlier, in 1664, the Danish physician, Nicolas Stenon, described the autopsy of a malformed embryo exhibiting a harelip with cleft palate, syndactyly, an abdominal wall schistasis, defects of the genitals, and a heart defect which Stenon described as *stenosis of the pulmonary artery, septal defect, and dextraposition of the aorta.* This description, quite possibly the first, of a congenital heart defect is of interest to us for the heart malformation here described was but one of numerous defects. We now know this to be a common finding in congenital heart disease (CHD).

In the survey of the literature to follow, we shall discuss the findings with regard to congenital heart disease under four broad headings, namely, (A) congenital heart defects with associated malformations, (B) congenital heart defects and heredity, (C) congenital heart defects and the influence of external factors on fetal development, and (D) the results of extensive surveys on congenital heart disease carried out prior to this date.

A. Congenital heart defects with associated malformations.—Malformations are frequently observed in association with heart disease. We might classify these associations as follows:

1. Syndromes of which CHD is but a part, such as the Ellis and van Crefeld, or Marfan's, or Kartagener syndrome.

2. Syndromes with which CHD is occasionally associated, such as Turner's syndrome (Tyler, et al., 1953, Vulliamy, 1953) or acrocephalosyndactyly (Owen, 1951).

3. CHD in individuals showing (a) another defect such as esophageal atresia (Aboud and Alfy, 1953), renal defect (Boland and Fitzgerald, 1952), a defect of the retinal blood vessels (Bonnet, 1954), a congenital absence of the spleen (Bush and Ainger, 1955), a megacolon (Demirağ, 1951), a diaphragmatic hernia (Lowys, et al., 1955), or a diaphragmatic aplasia (Cortese and Bettolo, 1955), or (b) many malformations (Bruyne, et al., 1952; Wolf, 1955).

4. CHD, usually an atrioventricularis communis, in association with mongolism. Granata, et al., (1952) observed a congenital heart defect in 24 out of 56 mongolians, and Evans (1950) reported CHD in 28 of 63 mongolians who came to autopsy before the age of five years.

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B. Congenital heart defects and heredity.—Multiple cases of CHD in a single family have been reported by numerous authors. A familial concentration, however, is not necessarily evidence of an hereditary etiology. Let us, nonetheless, summarize the conclusions suggested by these single family cases.

Gänsslen, Lambrecht and Werner (1940) surveyed the literature prior to 1940. Sixty-eight family pedigrees were studied by these authors. They cite evidence for recessive inheritance in certain cases, in particular patent ductus arteriosus and atrial septal defect, and for possible dominant inheritance in other traits. Other authors provide evidence for an intrafamilial homogeneity of the clinical type of CHD: patent ductus arteriosus (Kjaergaard, 1946), pulmonary stenosis (Coblentz and Mathivat, 1952), interventricular septal defect (Tucker and Kinney, 1945), etc. Other families, however, show no such intrafamilial homogeneity (Stein and Barber, 1945). All of the simpler modes of inheritance save sex-linkage have been suggested by various authors.

Situs inversus and dextrocardia have frequently been reported in related individuals as well as in twins. Doolittle (1907) described a family with two cases of dextrocardia and suggested the possibility of dominant inheritance. The same author finds no evidence, from other cases of situs inversus viscera or dextrocardia, of an increase in consanguinity, but he does point out the high frequency of twinning in families in which a case of dextrocardia has been observed. Furthermore, he reports eight cases of twin pairs in which only one twin exhibited dextrocardia. Doolittle believes that these cases of discordance in twins may afford an explanation of the mechanism of dextrocardia.

Torgersen (1948) reported 12 cases of dextrocardia in MZ twins (six of which were concordant) and three cases of concordant DZ twins. He believes that the discordant MZ twins do not support the hypothesis of a mirror mechanism since extrinsic factors acting on only one of the twins could produce discordance. He further asserts that the concordant MZ twins do not necessarily support the hypothesis of a genetic origin, since extrinsic factors may well influence both twins.

Lowe and McKeown (1954) report ten cases of dextrocardia and 20 cases of situs inversus. They estimated the frequency of isolated dextrocardia to be 1 in 29,000 births and that of situs inversus 1 in 7,000. Only one of their cases of situs inversus was familial. They also report one case of MZ twins discordant with respect to situs inversus and conclude that the trait is not inherited as if due to a single recessive gene with full manifestation, thus contradicting Cockayne (1938), who asserted that situs inversus is a recessively inherited trait and that there exist different types of partial transposition.

Other publications (Reinhardt, 1912; Pezzi and Carugati, 1924; Araki, 1935; Kean, 1942; Helweg-Larsen, 1947, 1948; Jeune and Confavreux, 1948) support the hypothesis that situs inversus and dextrocardia are due to a very complex genetic mechanism, and that mirror imaging with regard to these traits is a very frequent occurrence in twins. The occurrence of situs inversus or dextrocardia in single individuals may be due to the survival of only one of two such "mirror" twins.

Finally, cases of twins exhibiting CHD other than dextrocardia and situs inversus have been described by several authors (Gänsslen, et al., 1940; Benesova and Sikl, 1954; Bertoye, et al., 1952; Graves et al., 1954; Tumay and Gurson, 1952; McClintock, 1945; Morison, 1949; Wade, 1952; Goldman and Stern, 1952). Many more cases of MZ twins (of which approximately half are concordant and half are discordant) than DZ twins are found in the literature. This fact suggests that only those

cases which support a particular point of view or are uncommon findings are published, and of course, seriously limits the usefulness of the data; nevertheless the occurrence of discordant MZ twins attests to the role of non-genetic factors in the etiology of CHD. Morison (1949) believes that at an early embryonic stage twins compete with one another for nutrition and, as a consequence, one of them may suffer from a transitory lack of nutrition, which in turn leads to the occurrence of a malformation. The malformed twin may then be carried, as it were, to delivery by the non-malformed twin through the agency of a mutual circulation. Concordance in MZ twins may occur through the influence of extrinsic or genetic factors whereas uniform concordance in DZ twins would appear to suggest primarily extrinsic factors. A case of concordant DZ twins where the concordance is probably due to extrinsic factors has been reported by Bertoye, et al. (1952). On the whole, the published twin data might seem to suggest a greater importance of extrinsic factors than the genetic factors in the etiology of CHD.

C. Congenital heart disease and external factors influencing fetal development.—During the embryonic stage, non-genetic factors may either interrupt normal growth of the heart or provoke growth in an abnormal direction. Gregg (1941) demonstrated the influence of rubella on fetal development. Others confirmed his findings (Swan, et al., 1943, 1944; Carruthers, 1945; Reese, 1944; Rones, 1944; and Albaugh, 1945). The frequency of malformation among the offspring born to mothers having rubella has been variously estimated to be from 25 per cent to about 80 per cent.

Carruthers (1945) concluded that the severity of a malformation tends to decrease the later in pregnancy the infection occurs and Conte, McCammon, and Christie (1945) showed that rubella causes malformations only if the mother is affected during the first trimester of pregnancy. From data reported by Le Lorier (1955) in a survey of the literature, it would seem that the risk of malformation is 60 to 80 per cent if rubella occurs during the first trimester. However, other observations (Krugman and Ward, 1954; Logan, 1951) suggest that the risk is more likely of the order of 20 per cent.

In addition to rubella, other viral or non-viral diseases may be etiologic factors in congenital malformations. While Buck (1955) doubts that this is so, Landtmann (1948) has reported that in 45 per cent of 73 pregnancies terminating in the birth of a malformed child the mother had had a viral or non-viral disease during pregnancy (12 cases of acute disease, 4 of tuberculosis, 1 of jaundice, etc.), while in a control group of 200 mothers only 14 per cent reported similar episodes. We have reported elsewhere (Lamy et al., 1951) a high frequency of infectious diseases during pregnancies giving rise to malformed children.

Other external factors which possibly play a role in the etiology of CHD are maternal age and birth rank (MacMahon, 1952; Landtmann, 1948), birth interval (Murphy, 1947), the altitude of the birthplace (Alzamora, 1953), and the month of birth (Rutstein, et al., 1952). The latter report avers that the frequency of patent ductus is higher during the winter months (from October to January), and this may reflect the high frequency of rubella during the early months of such pregnancies (late winter, early spring).

D. Extensive Surveys.—At the present time extensive surveys on CHD would seem to us to be one of the more fruitful approaches to the etiology of CHD.

Such surveys yield information with regard to genetic factors as well as familial incidence, non-genetic factors, and the occurrence of unusual events during pregnancy.

McKeown, MacMahon, and Parsons (1953) have reported that 1.8 per cent of the siblings of 431 propositi distributed in 425 sibships exhibited CHD. This frequency was estimated to be 0.32 per cent in the general population. The authors did not observe an increase of CHD among the parents or the first cousins of the propositi. They observed a slight increase in the consanguinity rate only in the case of dextrocardia and situs inversus.

Richards, et al., (1955) have observed a CHD frequency of 0.83 per cent in a group of 6,053 infants. This frequency was shown to vary from 7.7 per cent in stillborn children or children dying during the first month of life, to 0.6 per cent in children who had reached the second month of life. These authors also noted that older mothers more frequently produce malformed children. They believe that neither external factors affecting fetal development nor genetic factors play a major role.

Anderson (1954) found in a study of 117 cases of patent ductus arteriosus that both genetic factors and extrinsic factors are important.

Polani and Campbell (1955) concluded from a study of 377 families with one or more cases of CHD that, (1) malformations of the aorta appear more frequently in boys than in girls, (2) the frequency of CHD is twenty times higher among the siblings of the propositi than in the general population, (3) the rate of consanguineous marriages was not increased among the parents of the propositi, and (4) there was no evidence for extrinsic factors such as maternal age, birth rank, or abnormalities during pregnancy.

Finally, we have, in earlier surveys (Lamy and Schweisguth, 1947, 1948; Schweisguth, 1952) reported evidence suggesting the importance of both genetic and extrinsic factors. This survey now encompasses 1,188 cases of CHD. The present paper will be devoted to a discussion of these cases.

MATERIALS AND METHODS

The 1,188 index patients with CHD here reported were examined during the years 1946 through 1955 by Professors Robert Debré and Pierre Soulié and their assistants at the "Consultation de Cardiologie de la Clinique Médicale de l'Hopital des Enfants Malades" in Paris. The medical information available for these 1,188 cases varies somewhat as indicated in Table 1. Briefly, in 72.6 per cent diagnosis has been established on clinical grounds with (1) X-ray examination and E.K.G. (all cases), and (2) catheterization (most cases); in 14.3 per cent a surgical operation confirmed a previous clinical diagnosis; and in 13.1 per cent death followed the first consultation and necropsy was performed in 61.9 per cent of these cases.

Each of the index cases, the propositus, has been assigned to one of the following eight clinical subgroups:

Group I: 238 cases (20.03%): Fallot's tetralogy and pentalogy.

Group II: 56 cases (4.71%): Pulmonary valvular stenosis either as a unique defect or accompanied by atrial septal defect.

Group III: 136 cases (11.45%): Patent ductus arteriosus with or without another heart defect.

Group IV: 143 cases (12.04%): I.V. septal defect.

Group V: 97 cases (8.16%): Atrial septal defect.

Group VI: 54 cases (4.55%): Coarctation of the aorta.

Group VII: 332 cases (34.04%): Precise diagnosis has either not been possible or the defect was extremely complex.

Group VIII: 132 cases (11.11%): Well defined but uncommon anatomical defects. Among these are:

1. Abnormal coronary arteries: 4 cases (0.36%): 2 ♂, 2 ♀
2. Atrioventricularis communis: 15 cases (1.26%): 5 ♂,10 ♀
3. Transposition of the great vessels: 23 cases (1.94%): 17 ♂, 6 ♀
4. Eisenmenger's complex: 20 cases (1.68%): 10 ♂, 10 ♀
5. Moderate truncular pulmonary atresia: 10 cases (0.84%): 1 ♂, 9 ♀
6. Valvular aortic stenosis: 16 cases (1.35%): 14 ♂, 2 ♀
7. Tricuspid atresia: 19 cases (1.60%): 10 ♂, 9 ♀
8. Dextrocardia: 13 cases (1.09%): 6 ♂, 7 ♀
9. Situs inversus with or without congenital heart disease: 12 cases (1.01%): 4 ♂, 8 ♀

The relative frequencies observed in this survey are certainly a biased estimate of the true frequencies at birth. In particular the frequencies of those types of CHD which cause death at a very early age are underestimated. This is of course inherent in the method of ascertainment and could only be overcome by a prospective study. Likewise, a prospective study based solely on surgical or post-mortem diagnosis would be the only study giving entire confidence in the diagnosis. But such a study would not encompass cases of CHD which do not lead to the operating or autopsy tables. In order to approach such ideal conditions we have classified each case in a particular group only on very firm diagnostic grounds, and cases which appeared slightly dubious were classified in group VII.

The following information was obtained for each of the 1,188 cases:

1. The propositus:
   a. Age at first consultation
   b. Sex
   c. Social status of parents
   d. Birthweight
   e. Diagnosis (clinical, surgical, post-mortem)
   f. Associated malformations
2. Propositus' parents:
   a. Consanguinity
   b. Mother's and father's ages
   c. Mother's and father's histories
   d. Information on mother's pregnancy
3. Propositus' siblings:
   a. Number of males, females, miscarriages, stillbirths, twins
   b. Congenital malformations
   c. Birth rank of propositus
4. Other relatives of the propositus:
   a. Number and relationship of malformed persons, if any

The above information was obtained either by direct questioning of the parents of the index cases, or by use of the patient's record in association with a supplementary mail questionnaire. When siblings of the propositi were reported to exhibit a CHD or any other defect the diagnosis was confirmed by clinical examination. In the case of more distant relatives a report was obtained from the attending physician.

Comparable information was obtained on a control group of 660 individuals randomly selected from the general population. To minimize possible extraneous differences between the two groups, special attention was directed toward ensuring comparable social and familial backgrounds, age of index cases, place of origin, etc. It should be pointed out, however, that the control group was drawn primarily from Paris, whereas the study group was drawn from all over France. This could adversely affect the consanguinity rate, but as we shall see, the rate observed in the control group compares favorably with that generally observed in France.

THE DATA

A. Age at first consultation.—Half of the patients with congenital heart disease were examined for the first time before the age of 3 years; the mean age at first examination for all patients was 3.62 years.

B. Sex ratio.—There were 605 males (50.92 per cent) and 583 females (49.03 per cent) among the 1,188 cases of CHD (Table 1). These figures agree with a theoretical sex ratio of 1:1 ($X^2 = 0.20$; $P = 0.60$) and with the sex ratio observed in the control group, namely, 335 males to 325 females ($X^2 = 0.01$; $P = 0.90$).

The sex ratio is not uniform, however, in all clinical subgroups. In Group III (patent ductus arteriosus) the sex ratio deviates significantly from 1:1 ($X^2 = 13.90$; $P = 0.0002$) as well as from the control. Patent ductus appears to occur, on the average, three times as frequently among females as among males (Table 1). In Group VI (coarctation of the aorta), the frequency of affected males is higher than affected females, although this difference is not significant ($X^2 = 2.44$; $P = 0.15$), and in Group VIII, the frequency of valvular aortic stenosis is significantly higher in males ($P = 0.024$). These results will be discussed in detail later.

C. Maternal age and birth rank.—Adequate information with regard to maternal age and birth rank is available for 1,177 cases in the CHD group, and all of the cases in the control group. The mean maternal age for the CHD group, in its entirety, is lower than that for the control group, but not significantly so (28.39 years vs. 28.84 years) (Table 2). Mean birth rank, on the other hand, is significantly different between the groups, with the CHD group having a mean of 2.23 whereas the control group has a mean of 2.03 ($t = 2.92$, $P = 0.01$).

Among the eight clinical subgroups, the mean maternal ages and mean birth rank show little variation when compared with the entire CHD group.

In Table 3 are given the results of the test of the independence of maternal age and birth rank effects. When birth rank is held constant, maternal age is lower in the CHD group than in the control group (except for rank 6). This difference is significant, however, only for ranks 1 and 2 ($t = 2.24$ and 2.27, $0.01 < P < 0.05$). If maternal age is held constant, birth rank is significantly higher in the CHD group for maternal age intervals 25–29, and 30–34 ($t = 3.11$ and 2.62, $P < 0.01$).

Paternal age was accurately known for 779 of the index cases. Mean paternal age for these cases (Table 4) was 31.13 years and mean maternal age, in the same group, was 28.23 (in the entire group, mean maternal age was 28.39). In the control group, mean maternal age was 28.86 and mean paternal age was 30.80 years. The difference between the two mean paternal ages is not significant ($t = 0.84$, $P = 0.40$). Significant differences do exist, however, between the father-mother age correlation coefficients in the two groups. In the CHD group, $r = 0.75$ and in the control group $r = 0.56$ (Table 4).

D. Consanguinity.—In Table 5 are given the data concerning relationship be-

TABLE 1. DISTRIBUTION OF CONGENITAL HEART DEFECTS BY SEX, AGE AT FIRST CONSULTATION, AND TYPE OF DIAGNOSIS (CLINICAL, OPERATIVE, AUTOPSIES)

Clinical Group	Sex	Clinical dx.	Operative dx.	Deaths[1]	Total[2]
I. Fallot's tetralogy and pentalogy	♂	65	50	16(9)	131(55.04)
	♀	53	33	21(11)	107(44.96)
	Tot.	118	83	37(20)	238(20.03)
II. Pulmonary valvular stenosis	♂	18	6	5(3)	29(51.78)
	♀	16	5	6(5)	27(48.22)
	Tot.	34	11	11(8)	56(4.71)
III. Patent ductus arteriosus	♂	16	21	1(1)	38(27.94)
	♀	63	34	1(1)	98(72.06)[3]
	Tot.	79	55	2(2)	136(11.45)
IV. I.V. septal defect	♂	72	0	7(4)	79(55.24)
	♀	63	0	1(1)	64(44.76)
	Tot.	135	0	8(5)	143(12.04)
V. Atrial septal defect	♂	40	1	2(0)	43(44.33)
	♀	52	0	2(2)	54(55.67)
	Tot.	92	1	4(2)	97(8.16)
VI. Coarctation of the aorta	♂	23	9	3(1)	35(64.81)
	♀	14	3	2(1)	19(35.19)
	Tot.	37	12	5(2)	54(4.55)
VII. CHD with no precise diagnosis	♂	152	1	28(17)	181(54.52)
	♀	124	2	25(13)	151(45.48)
	Tot.	276	3	53(30)	332(34.04)
VIII. Uncommon anatomical defects	♂	45	4	20(16)	69(52.27)
	♀	47	1	15(11)	63(47.73)
	Tot.	92	5	35(27)	132(11.11)
Total CHD group	♂	431	92	82(51)	605(50.92)
		49.94	54.11	53.90(53.13)	
	♀	432	78	73(45)	583(49.08)
		50.06	45.89	47.10(46.87)	
	Tot.	863	170	155(96)	1188(100.00)
		72.64	14.31	13.05(61.94)	

[1] The figures in parentheses refer to the number of autopsies.

[2] The second figures in the "♂" and "♀" rows refer to the percentage of each sex, and they add to 100, while the second figure in the "Tot." row refers to the percentage of each clinical group with regard to the total CHD group.

[3] The sex-ratio is significantly different from 1:1 ($P < 0.01$).

tween the parents of the propositi. In each case, the coefficient of relationship, C, has been calculated, where

$$C = \sum \left(\tfrac{1}{2}\right)^n$$

and n is equal to the number of links in the ancestral chain joining the two parents and passing through a common ancestor, and summation is over all different paths connecting the parents. To obtain a total coefficient of relationship, say $\bar{C}$, for each of the eight clinical groups, as well as for the total CHD and control groups, the individual coefficients have been summed, and divided by N, the total number of matings in the particular group.

TABLE 2. MEAN MATERNAL AGE AND MEAN BIRTH RANK IN EACH CLINICAL SUBGROUP, IN THE TOTAL CHD GROUP, AND IN THE CONTROL GROUP

	I	II	III	IV	V	VI	VII	VIII	Total	Control
N	233	55	135	143	96	53	331	131	1177	660
Mean Maternal age	28.25	29.40	28.30	28.00	28.65	27.85	28.40	29.00	28.39	28.84
Standard error of the mean, $s_{\bar{x}}$	0.41	0.82	0.59	0.51	0.71	0.84	0.36	0.53	0.19	0.24
Mean birth rank	2.25	2.35	2.14	2.10	2.04	1.98	2.35	2.32	2.23	2.03
$s_{\bar{x}}$, id	0.10	0.20	0.14	0.11	0.14	0.12	0.09	0.13	0.04	0.05

TEST OF SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS OF TOTAL CHD GROUP AND CONTROL GROUP

	Mean Maternal Age	Mean Birth Rank
d (difference)	0.45	0.194
s_d	0.31	0.066
t	1.47	2.920

Two findings emerge from a comparison of the total coefficients of relationship, namely, (1) consanguinity is 3.6 times higher in the CHD group than in the control group, and (2) $\bar{C}$ varies considerably from one clinical subgroup to another. It is highest in situs inversus, very high for atrioventricularis communis and dextrocardia, and is lowest in Group I (Fallot's tetralogy).

Analysis of the 28 sibships arising from consanguineous matings showed the following:

(1) In 2 cases (7.1%) a sibling of the propositus was also suffering from CHD. In the entire group of 1,188 sibships, this frequency was only 2.5 per cent. Though the observed difference is not significant, it may be that the frequency of malformed children is increased among the offspring of related parents.

(2) In 5 cases (17.8%) the propositus exhibited a malformation in addition to CHD. In all 1,188 propositi, this frequency was also 17.8 per cent. Hence consanguinity does not appear to increase the frequency of additional malformations.

(3) In 3 cases (10.7%), a sibling of the propositus exhibited a malformation other than a heart disease whereas in the whole group of 1,188 sibships this frequency was only 0.93 per cent (20 out of 2045). The difference between these two frequencies is significant ($P < 0.05$).

(4) The frequency of all individuals (propositi excluded) exhibiting a congenital heart disease or another malformation was 17.8 per cent in consanguineous sibships, whereas this frequency was only 2.4 per cent (50/2045) in all 1,188 sibships. The difference between these two values is significant ($P < 0.05$).

Collectively, these observations suggest that consanguinity increases the frequency of all malformations, and only secondarily the frequency of congenital heart disease. It would also seem that this increase does not influence the number of malformations possessed by a single individual.

E. Infection, threats of miscarriage and premature delivery, and other abnormalities during pregnancy.—Some 232 (19.5%) of the 1,188 mothers in the CHD group have reported unusual events during the pregnancies terminating in the index cases. In the control population, only 72 (10.9%) of the 660 mothers reported similar events. These two frequencies are significantly different ($P < 0.001$), and suggest

TABLE 3. TEST OF INDEPENDENCE OF MATERNAL AGE AND BIRTH RANK EFFECTS

Birth Rank..	1		2		3		4		5		6		7		Total		CHD		Control		t
Age of Mother	CHD	Control	CHD	Control	CHD	Control	CHD	Control	CHD	Control	CHD	Control	CHD	Control	CHD	Con-trol	Mean birtn rank	$s_{\bar{x}}$	Mean birth rank	$s_{\bar{x}}$	
15–19	56	10	7	3		1	1								64	14	1.16	0.06	1.35	0.11	1.01
20–24	198	101	78	40	18	16	6	1	1		1				302	158	1.46	0.04	1.47	0.06	0.14
25–29	136	124	111	62	70	29	22	10	7	4	2	2	1		349	231	2.04	0.06	1.76	0.07	3.11
30–34	52	40	67	56	55	27	38	12	16	2	5	7	5	1	238	145	2.72	0.09	2.34	0.11	2.62
35–39	39	12	30	18	33	16	22	13	8	3	9	3	14	5	155	70	3.08	0.15	3.08	0.19	—
40–44	13	4	9	9	8	9	12	4	10	1	4	1	10		66	28	3.74	0.22	2.71	0.23	2.00
45+		3		3		1		1		2			3	4	3	14	7.00	—	3.86	0.68	—
Total	494	294	302	191	184	99	101	41	42	12	21	13	33	10	1177	660					
Mean age	25.55	26.45	28.05	29.25	30.45	31.15	32.45	33.40	34.25	34.50	35.10	33.15	38.36	40.50							
$s_{\bar{x}}$	0.27	0.29	0.31	0.43	0.38	0.42	0.55	0.85	0.86	2.09	1.16	1.08	0.83	1.65							
t	2.24		2.27		1.22		1.83		0.11		1.43		1.22								

TABLE 4. MEAN MATERNAL AGE AND MEAN PATERNAL AGE. COEFFICIENTS OF CORRELATION

	Maternal Age		Paternal Age	
	Control	CHD	Control	CHD
N	660	779	660	779
Mean age	28.86	28.23	30.80	31.13
σ	6.09	6.24	7.38	7.37
s	0.24	0.22	0.29	0.26
t			0.84	
r	0.564		0.749	

Significance test for difference of correlation coefficients t (z transformation) = 7.45 and P = 0.007

TABLE 5. THE MEAN COEFFICIENT OF RELATIONSHIP ($\bar{C}$) AMONG THE PARENTS OF THE PROPOSITI BY CLINICAL SUBGROUPS AND FOR THE CONTROL

CHD Group	N	Relationship of parents	$\bar{C} \times 10^3$
I	238	1 third cousin 1 second cousin once removed	0.098
II	56	2 first cousins	4.464
III	136	1 first cousin once removed 2 first cousins	2.298
IV	143	1 first cousin	0.874
V	97	3 first cousins	3.866
VI	54	1 second cousin	0.579
VII	332	1 brother-sister 5 first cousins 1 second cousin once removed 1 third cousin	3.459
VIII			
Situs inversus	12	1 first cousin 1 second cousin 1 first cousin once removed	18.170
Dextrocardia	13	1 first cousin	10.420
Eisenmenger's complex	20	1 first cousin 1 second cousin	7.820
I.A.V. Communication	15	1 first cousin 1 second cousin	10.420
Total	1188		2.460
Control	660	3 first cousins 2 second cousins 1 third cousin	0.6748

that abnormal symptoms during pregnancy may be twice as common in the CHD group as in the control group.

This difference could, of course, reflect a tendency for mothers giving birth to abnormal children to seize upon unusual events to account for the abnormality in their child. It seems unlikely, however, that this explanation would account for all of the difference which has been observed, since every effort was made to elicit positive histories from the control group.

1. Rubella.—Fourteen cases of rubella, of which 11 were positively diagnosed and 3 were very probably rubella, occurred during the early stages of pregnancy, 10

TABLE 6. THE FREQUENCY OF ABNORMALITIES DURING PREGNANCY BY MATERNAL AGE

(The figures in parentheses under the figures defining the age groups refer to the number of propositi in each maternal age group; the figure on the left refers to the CHD group, that on the right to the controls.)

Maternal Age Group	Rubella				Threats of miscarriage and premature delivery				Infections				Other abnormalities				Total			
	CHD		Control		CHD		Control		CHD		Control		CHD		Control		CHD		Control	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
15–19	2		0		4		1		2		0		6		3		14		4	
(64) (14)		3.13				6.25		7.14		3.13				9.38		21.42		21.87		28.56
20–24	4		0		18		8		21		6		18		7		61		21	
(302) (158)		1.32				5.96		5.06		6.95		3.80		5.96		4.43		20.20		13.29
25–29	7		0		21		6		22		5		25		10		75		21	
(349) (231)		2.01				6.02		2.60		6.30		2.16		7.16		4.32		21.49		9.09
30–34	0		0		16		6		8		3		17		6		41		15	
(238) (145)						6.72		4.14		3.36		2.07		7.14		4.14		17.23		10.35
35–39	1		0		6		2		8		2		15		2		30		6	
(155) (70)		0.65				3.87		2.86		5.16		2.86		9.68		2.86		19.36		8.58
40–44	0		0		2		2		4		0		5		3		11		5	
(66) (28)						3.03		7.14		6.06				7.56		10.71		1.67		17.85
45+	0		0		0		0		0		0		0		0		0		0	
(3) (14)																				
Total.....	14		0		67		25		65		16		86		31		232		72	

during the first month, 3 during the second month, and 1 in the third month. No cases were observed after the third month, nor were any cases observed in the control group at any time.

The frequency of rubella varies considerably from one subgroup to another. In 5 of the 14 cases, the pregnancy terminated in an infant with patent ductus arteriosus although the general frequency of this defect is only 11.45 per cent.

2. Threats of miscarriage and premature delivery.—Such symptoms occurred in 67 pregnancies (5.64%) in the CHD group whereas among the control group, the comparable figure was 3.64 per cent. The difference between these two frequencies is greater when only the first month of pregnancy is taken into account—4.13 per cent in the CHD group as opposed to 1.66 per cent in the control group.

The frequency of "threats of miscarriage" varies in the different maternal age groups. They are twice as frequent among mothers under 35 years of age as among mothers over 35 years. In the control group, the frequency of "threats of miscarriage" remains constant in the different maternal age groups (Table 6). It would seem that (a) the threat of miscarriage occurs twice as frequently in pregnancies terminating in a malformed child as in pregnancies terminating in a normal child, and (b) in the study group, the threat of miscarriage is twice as common among young mothers (under 35) as among older mothers (over 35).

3. Infections.—The frequency of infection during pregnancy is twice as high in the study group as in the control group. In most cases, the diagnosis during pregnancy of a microbial or viral infection other than rubella was made by a physician at the time of the prenatal examinations required by law. Among the latter infections recorded are measles, grippe, typhoid fever, pleurisy, E. coli infection of the urinary tract, tuberculosis, etc. Sixty-five such cases were observed (5.47%) in the CHD group whereas in the control only 16 mothers (2.42%) were observed to have had infections of this variety.

In the CHD group, episodes of infection were highest during the first month of pregnancy (20 cases) and decreased steadily thereafter (15 cases in the second month, 7 cases in the third month, and 1 case which persisted throughout the first trimester). In all, 43 cases were observed during the first three months of pregnancy. In the control group, 12 of the 16 cases of infection (of which 7 were E. coli infections of the urinary tract) were recorded during the first trimester of pregnancy. By and large, the infections experienced by the CHD group during the first trimester were more serious than those in the control group. After the first three months, the two groups were comparable.

4. Other unusual events during pregnancy.—With regard to other irregularities during pregnancy, we observed 11 cases of persisting menses in the CHD group (only 1 in the control); traumas (surgical operations, falls, etc.) in the CHD group were eleven times (11 cases vs. 1) as high as in the control group during the first three months, and six times (6 cases vs. 2) higher during the last two trimesters. It is worth noting that eight cases of systemic hormonal treatment without any threat of pregnancy interruption were observed among the mothers of the CHD patients. In one case, this treatment was instituted because of a history of frequent miscarriage. One case of treatment with ultraviolet rays during the first seven months without interruption of the pregnancy was observed. Sixteen cases of incurable vomiting, 9 cases of grave emotional shock, and 13 of other unusual events were also observed among the mothers of the CHD propositi.

5. The different clinical groups.—The groups do not show the same frequencies

TABLE 7. FREQUENCY OF CHD CASES AMONG THE SIBLINGS OF THE PROPOSITI

	Clinical type of Congenital Heart Disease								
	I	II	III	IV	V	VI	VII	VIII	Total
Number of siblings	404	107	249	213	161	78	594	239	2045
Number of affected siblings	4	4	3	1	2	2	13	1	30
Per cent	1.0	3.74	1.2	0.47	1.24	2.56	2.19	0.42	1.46

of irregularities during pregnancy. The greatest frequency (25%) of irregularities was observed in Group III (patent ductus arteriosus) and as mentioned, this group has the greatest frequency of rubella. In Groups I and IV (Fallot's tetralogy, and I.V. septal defect respectively) the frequencies were almost identical (22.3 and 22.4%). Among the remaining clinical subgroups, the frequency decreases in this order: Group V (atrial septal defect), VII (unspecified heart diseases), VI (coarctation of the aorta), VIII (miscellaneous), and II (pulmonary valvular stenosis).

F. Familial incidence of congenital heart disease.—

1. In the sibship.—Table 7 presents the familial incidence of congenital heart disease for each clinical subgroup as well as for the total CHD group. Among the siblings of the propositi, 30 cases of CHD have been registered (Tables 7 & 8). In no instance does the per cent of affected individuals approach that to be expected under a hypothesis of a single, fully penetrant gene. This is hardly an unexpected finding.

While the data are not compatible with a simple genetic explanation, the incidence of CHD among the siblings of the propositi is elevated in all clinical subgroups over that of the control group. In the control group we did not observe a single instance of congenital heart disease among the 1,487 offspring distributed among the 660 sibships. Since our data do not permit a precise estimate of the frequency of CHD in the general population nor are there other estimates in the French literature, we shall accept the incidence given for England by Polani and Campbell (1955) of 1 case per thousand individuals. This rate would lead to an expected number of 1.48 affected persons in our control group. The probability of observing no cases among the 1,483 individuals in the control if the true rate is 0.001 is approximately 0.23.

Other frequency estimates of CHD in the general population have been proposed. Anderson (personal communication) believes that the true frequency is approximately 0.7 per cent. This figure would not be in agreement with the control group. However, even if it should be so, one may conclude that the frequency of congenital heart disease is elevated among the siblings of affected individuals. While this elevation is not consistent with that to be expected on a single gene hypothesis, the elevation may amount to a seven-fold increase in the disease rate if one accepts 0.7 per cent as the frequency of CHD in the general population.

2. Among the parents.—In both CHD and control groups we failed to observe a single instance of congenital heart disease among the parents of the index cases.

3. Among the first cousins of the propositi.—In the CHD group 20 cases of heart malformation have been observed (Table 8). The total number of first cousins is not sufficiently well known, however, to permit computing a frequency. In the control group, only one case, Fallot's tetralogy, has been observed. Since the ratio of propositi, to control cases is 2:1 while the ratio of secondary cases in these two groups is 20:1,

TABLE 8. CONGENITAL HEART DEFECTS IN THE RELATIVES OF THE PROPOSITI

Group	Sibship[1]		1st cousins		Description of CHD
	Same	Other	Same	Other	
I	2		2		Fallot's tetralogy
		2			Unspecified CHD
II	1				Pulmonary valvular stenosis
		1			Fallot's tetralogy
		2			Unspecified CHD
III		3			Unspecified CHD
			1		Patent ductus arteriosus
				3	Tetralogy—I.V. septal defect—unspecified
IV	1		1		I.V. septal defect
		½ sister		2	Unspecified CHD
				1	Fallot's tetralogy
V	1		1		Patent foramen ovale
		1		1	Fallot's tetralogy
VI	1				Coarctation of the aorta
		1			Fallot's tetralogy
VII		1			Aorta-pulmonary communication
		1			Patent ductus arteriosus
		1		2	Fallot's tetralogy
		½ sister			Fallot's tetralogy
		2			Fallot's tetralogy (2 brothers)
		8		5	Unspecified CHD
VIII	1				Eisenmenger's defect (as in propositus)
Total.....	7	25	5	15	
Control.....			1		Fallot's tetralogy

[1] The headings "Same" and "Other" indicate whether the clinical type of CHD observed in the relatives of the propositus was or was not of the same type as in the propositus.

it is very likely that the frequency of congenital heart disease is increased among the cousins of the index cases.

4. The clinical similarity of multiple cases of congenital heart disease within a family. —When a heart malformation occurs among the siblings, or other relatives of the propositus, it is generally not of the same clinical or anatomical type as the malformation found in the propositus. We have observed (a) only 7 cases (out of 30) where propositus and sibling possessed the same malformation, (b) 5 cases (out of 20) where the propositus and a first cousin had the same malformation, and (c) 4 cases (out of 43) where the propositus and some relative other than parent, sibling, or first cousin exhibited the same congenital malformation of the heart. On the average, then, when a relative of the propositus has a congenital heart disease the disease is of the same variety as that exhibited by the propositus in only 1 out of 4 cases. These facts suggest that there is a familial increase in the frequency of congenital heart disease but this increase is non-specific. However, it should be borne in mind that the adequacy of the diagnosis of CHD among the relatives is not on a par with that in the propositi.

TABLE 9. CONGENITAL DEFECT IN ADDITION TO CHD PRESENT IN THE PROPOSITI

Type of defect	I	II	III	IV	V	VI	VII	VIII	Total CHD Group	%	Control
Mongolism	7		2	5	5		17	16	52	24.53	
Angiomatosis and nevi	1	2		2	4	1	4		14	6.60	3
Kyphoscoliosis		1	2	2	2		6	1	14	6.60	
Psychomotor retardation	5	1	2		2		1		11	5.19	
Multiple malformations of hands and upper limbs	3		1		2	1	1	1	9	4.25	
Bony chest deformities			1	1	2		2	1	7	3.30	
Cataract and other multiple defects		1	2				4		7	3.30	
Cataract			2	1			3		6	2.83	
Harelip and cleft palate	3					1	2		6	2.83	1
Club foot	1				1		3	1	6	2.83	
Severe multiple malformations	1			1			4		6	2.83	
Defect of the alimentary canal and associated organs	1			2			2		5	2.36	
Cranial malformations					1		4		5	2.36	
Facial hemiatrophy and paralysis of VII nerve	1			1	1			1	4	1.89	
Subluxation of the hip	1		1		1		1		4	1.89	
Ichthyosis	2			1			1		4	1.89	
Deaf-mutism		1		1				1	3	1.42	
Cataract and deafness			1				2		3	1.42	
Gross brain defects and severe mental deficiency	1			1			1		3	1.42	
Pyloric stenosis		1	1	1					3	1.42	
Hypospadias	1		1				1		3	1.42	
Spina bifida and associated malformations	1				1			1	3	1.42	
Syndactyly (hands and feet)	1						2		3	1.42	
Congenital torticolis	1		1	1					3	1.42	
Epilepsy					2				2	0.94	
Hydrocephaly and multiple cranial malformations	1						1		2	0.94	
Oxycephaly and multiple defects		1					1		2	0.94	
Gothic palate	1		1						2	0.94	
Bilateral palpebral ptosis							2		2	0.94	
Endocrine disorders			2						2	0.94	
Klippel-Feil syndrome								1	1	0.47	
Turner's syndrome						1			1	0.47	
Paralysis	1								1	0.47	
Language disorder							1		1	0.47	
Anodontia and multiple defects	1								1	0.47	
Bilateral congenital absence of the ears (anotia)							1		1	0.47	
Malformations of the ear							1		1	0.47	

TABLE 9—*Continued*

Type of defect	I	II	III	IV	V	VI	VII	VIII	Total CHD Group	%	Control
Congenital absence of soft palate							1		1	0.47	
Craniopharyngioma								1	1	0.47	
Supernumerary salivary gland		1							1	0.47	
Infantile glaucoma			1						1	0.47	
Cervical rib	1								1	0.47	
Multiple exostoses							1		1	0.47	
Lipomatosis			1						1	0.47	
Severe hypotonia					1				1	0.47	
Hypertrophy of the clitoris					1				1	0.47	
Congenital stridor (laryngeal malformation?)											1
Total	36	9	22	20	26	4	70	25	212	100.00	5
Per cent	15.13	16.07	16.18	13.99	26.80	7.41	21.08	18.94	17.85		

G. Other congenital malformations.—

1. In the propositus.—Some 17.9 per cent of the propositi exhibited a second congenital malformation (Table 9). Among the common second defects observed were mongolism (generally in association with atrioventricularis communis), cataract and deaf mutism (often, presumably, on the basis of rubella), harelip and cleft palate, and angiomatosis. The frequency of multiple defects varies considerably from one clinical subgroup to the next. The greatest frequency noted was in Group V (atrial septal defect—26.8%), and lowest in Group VI (coarctation of the aorta —7.4%).

In studying the role of maternal age in the etiology of multiple defects, we noted that if cases of mongolism were not excluded, the frequency of multiple defect increased more or less linearly with mother's age up to ages 35–39, but in age group 40–44 the frequency has almost doubled over that observed in ages 35–39 (19.8%) (Table 11). If cases of mongolism were excluded, however, the frequency of multiple defect did not increase with maternal age, and was, on the average, 13.5 per cent.

In the control group, the frequency of primary defect is very low, 0.76 per cent, (5 cases of angiomatosis, 1 of harelip and cleft palate, and 1 of congenital stridor), and it was impossible to ascertain with any measure of reliability the frequency of multiple defect.

2. In the sibships of the propositi.—The frequency of malformations other than congenital heart disease was 0.98 per cent (20 out of 2,045 siblings). In the control group, this frequency was 1.09 per cent (9 out of 823) (Table 10). There is little evidence, then, for a difference between these two groups. The frequency of congenital malformations in the general population is not well known in France. An estimate of 1–2 per cent seems a good approximation yet a recent study by Wallace and co-workers (1956) gives, for New York, an overall incidence as low as 8.9 per 1000 live births. Therefore our finding of 1 per cent malformations other than CHD, in the siblings of the propositi, are not unusual.

3. In the parents of the propositi.—We have observed 10 cases in the CHD group

TABLE 10. DEFECTS (OTHER THAN CHD) IN THE RELATIVES OF THE PROPOSITI

Group	Sibship	Parents	1st cousins	Description of the defect
I	1	1		Hemophilia (father and brother)
		2		Harelip (father)
		1		Diabetes
		1		Hydrocephaly
			6	Mental retardation; harelip; other malformation
II				
III	2			Bilateral club foot
	1			Angiomatosis
	1			Congenital torticolis
		1		Diabetes
IV	1			Gross malformation of the abdomen
	1			Malformations of the hands
		1		Cleft palate
			1	Malformations of the hands
			2	Harelip
			4	Various malformations
V			1	Harelip and spina bifida
			1	Mental retardation
VI	1			Multiple defects
VII	1			Bilateral palpebral ptosis
	1			Hemogenia (sister)
	3			Encephalopathy
	1			Harelip
	1			Club feet
	1			Angiomatosis
	1			Mental retardation
		1		Harelip
			6	Harelip
			4	Various malformations
VIII	2			Club feet (brother and sister)
	1			Club feet
		1		Subluxation of the hip
		1		Diabetes
Total	20	10	25	
Controls	1			Mental retardation
	1			Harelip and cleft palate
	1			Hypospadias
	2			Barrel chest (two brothers)
	3			Mutism (three brothers)
	1			Idiocy
			1	Supernumerary hemivertebra

where one parent was malformed, with fathers and mothers equally often affected; in the control group, no cases of malformations among the parents were recorded (Table 10).

4. In the first cousins.—The frequency of congenital anomalies among the first cousins of the index cases cannot be given with accuracy because the total num-

TABLE 11. FREQUENCY OF OTHER DEFECTS IN THE PROPOSITI BY MATERNAL AGE WITH AND WITHOUT THE INCLUSION OF CASES OF MONGOLISM

Maternal age group	15–19	20–24	25–29	30–34	35–39	40 44	45+	Total
N	64	305	352	240	157	67	3	1188
Other defects	9	47	59	41	31	24	1	212
Per cent	14.06	15.41	16.76	17.08	19.75	35.82	33.33	17.84
Number of mongols	1	6	6	10	14	14	1	52
Per cent among non-mongols	12.50	13.44	15.05	12.91	10.82	14.92	0	13.46

TABLE 12. A DESCRIPTION OF THOSE CASES WHERE THE PROPOSITUS IS ONE OF TWINS OR TRIPLETS

Group	Index Case is a Male	Index Case is a Female
I		
II	DZ brother, died at 5 wks.; no cyanosis, but murmur and edema.	Triple birth (♀ ♀ ♂); the two twins died at 5 wks. from infection.
III		
IV	One MZ brother normal; one dead fetus expelled. One brother of unknown zygosity. Normal. One MZ brother. Normal.	One sister of unknown zygosity died of accident. Normal.
V	One MZ brother. Normal.	Triple birth (♀ ♀ ♀); two fetuses expelled during pregnancy.
VI		One DZ sister; no CHD but convulsions. One brother. Normal.
VII	One sister. Normal. One sister. Normal. One brother of uncertain zygosity, yet both are CcDE.	One sister of unknown zygosity; died at 8 days. One MZ sister; no CHD but Little's disease. One sister died before birth. One sister MZ; normal. One sister of unknown zygosity.
VIII	One MZ brother. Normal. One MZ brother. Normal. One DZ brother. Normal.	One brother. Normal.
Control	One DZ brother. Normal. One brother of unknown zygosity, dead; premature, 6 months.	One MZ sister. Normal. One MZ sister. Normal. One MZ sister. Normal.

ber of first cousins is not known. However, 25 cases of malformations have been observed in the CHD group and only 2 cases in the control group (Table 10). This might suggest a higher frequency in the CHD group.

H. Multiple births.—Among the 1,188 propositi there were 22 unrelated individuals resulting from multiple births of which 19 were twin births and 3 were triplet births (Tables 12 and 13). In the control population, we observed 5 cases of twinning among the 660 propositi and no cases of triplets. The frequency of twins in both groups is low when compared to the frequency of twins at birth. This fact may be explained by our method of ascertainment which includes only children

TABLE 13. CONCORDANCE OR DISCORDANCE WITH RESPECT TO CHD IN MULTIPLE BIRTHS BY CLINICAL SUBGROUP

Group	ZYGOSITY								
	MZ			DZ			? Dx		
	Concordant	Discordant	?	Concordant	Discordant	?	Concordant	Discordant	?
I									
II				1	1*				
III									
IV		2*			1			1	
V		1							1*
VI					2				
VII		2			2			1	3
VIII		2			2				
Total: 22.....	0	7	0	1	8	0	0	2	4

* = Triplets.

having passed the early years of life in which mortality is known to be higher among individuals from multiple births than among those from single births. This bias, due to ascertainment, is introduced in both the CHD and control groups, hence we may justifiably compare them with regard to the frequency of twins and triplets. The total X^2 computed with Yates' correction is equal to 3.30, with two degrees of freedom and $P = 0.20$. Thus the frequency of multiple births is not elevated in the CHD group when compared to the control. Yet the frequency of triplets is high, and this may suggest a predisposition to malformation in multiple births involving more than two individuals.

Further study of the twins reveals the following: (a) Of seven presumably MZ twin pairs diagnosed by the usual morphological criteria in no instance were both twins affected, and (b) of the nine DZ twin pairs in only one instance was the co-twin affected. In six cases, a precise diagnosis of the type of twinning was not available. Among the latter pairs, two showed discordance, and four were uncertain because of neonatal death of the co-twin of the propositus.

DISCUSSION

A. The role of genetic factors in the etiology of CHD.—Sex ratio, for convenience, may be discussed here although association with sex does not necessarily imply genetic determination. Females more frequently than males have patent ductus arteriosus (3 girls to 1 boy, on the average) or moderate truncular pulmonary atresia (9 girls to 1 boy). It is interesting to note that these defects may be embryologically related, since the first involves the distal end of the sixth aortic arch and the other the proximal portion of the same arch. Aortic malformations appear to be more frequent in males, particularly coarctation of the aorta. In this connection, Polani and Campbell (1955) have observed a significantly higher frequency of males with Fallot's tetralogy. Our data suggest a similar trend but the increase is not statistically significant. The reason for these particular discrepancies with regard to the sex ratio is not clear since the sex ratio in the total sample is normal. As Polani and Campbell have pointed out, the hypothesis of a differential fetal death rate in the two sexes raises more questions that it resolves.

The general frequency of congenital heart disease is not known in France, but if we accept Polani and Campbell's English estimate of 0.1 per cent, the frequencies observed in the siblings of the CHD propositi are ten, twenty, and even thirty times higher depending upon the clinical subgroup. Specifically, we find that the frequency of heart malformations among the siblings of the propositi is, on the average, 1.47 per cent, and is noticeably elevated in pulmonary valvular stenosis (3.74%) and in coarctation of the aorta (2.56%). Even if the general frequency of CHD is higher, 0.7 per cent as Anderson has suggested, we note an increase which is twofold in the entire CHD group and may be as high as sevenfold in clinical subgroups. No striking elevation is observed in I.V. septal defect or Fallot's tetralogy. It must be emphasized, however, that in 23 cases out of 30 the clinical type of heart malformation exhibited by the propositus is not the same as that of his affected sibling. This suggests that if the high familial incidence of congenital heart disease is real, there is little in the way of intra-family specificity of type of malformation.

Consanguineous marriages are significantly more frequent in the CHD group than in the control, the latter reflecting the incidence in the general population. The consanguinity rate varies in the different clinical subgroups, being highest in pulmonary valvular stenosis and atrial septal defect, and lowest in Fallot's tetralogy, interventricular foramen, and coarctation of the aorta.

The siblings of the propositi from the consanguineous matings exhibit an elevated incidence of heart malformations, but this appears merely to reflect an increase in the over-all rate of malformations. This finding is in agreement with our observations that (1) in the event of multiple cases of heart malformations in a family, the malformations are dissimilar in type, and (2) the frequency of multiple defects in the propositus as well as his siblings is increased.

The 22 cases of twins here reported hardly support the hypothesis that congenital heart diseases are hereditary. Of seven MZ pairs, none showed concordance, while out of nine DZ pairs, one showed concordance.

In summary, certain findings, namely, the high consanguinity rate and the elevated familial incidence, suggest the importance of hereditary factors in the etiology of CHD, but the familial incidence is of a nonspecific variety. Nevertheless, as will be discussed later, this is evidence for ultimate genetic determination.

B. The role of non-genetic factors in the etiology of CHD.—Non-genetic factors such as maternal age, birth rank, irregularities during pregnancy, and time of year of birth, have been deemed important in the etiology of CHD by a number of authors (reviewed in the introduction). Our data provide further information with regard to these factors.

In agreement with Polani and Campbell but in disagreement with Richards, our analysis of maternal age failed to reveal a significant effect on the incidence of congenital heart disease. The birth rank data, however, reveal a significant difference, the mean birth rank being slightly higher in the CHD than in the control group.

The frequency of any irregularity during pregnancy is twice as high in the CHD group as in the control group. When we inquire into the sorts of irregularities which occur, we find that viral infections in general, but rubella in particular, are common events during the course of pregnancy in the CHD group. Moreover, the threat of interruption of pregnancy generally in the first three months is appreciably more common (two times) in the CHD than in the control group. This raises a number of questions with regard to cause and effect relationships assuming, of course, that the observed difference is real and that cause and effect relationships do exist. For example, we might ask whether or not the threat of interruption represents a "ma-

ternal defense" mechanism. In this connection, we note that among older mothers (over 35) the frequency of these accidents is only half that to be found in younger mothers. We might wonder whether this means that older mothers react less or whether factors provoking a threat of pregnancy interruption in young mothers lead to complete miscarriages in older mothers. Either of these alternatives could account for our observations. Irrespective of their interpretation, these observations question the advisability of interfering with the course of a spontaneous miscarriage.

Rutstein et al. claimed, on a sample of approximately 12 cases of patent ductus arteriosus, that a higher incidence of patent ductus occurred during the winter months. The distribution of CHD cases by month of birth showed no seasonal effect in our sample but lack of reliable figures with regard to the seasonal distribution of rubella in France did not allow us to draw any conclusions with regard to this point. The frequency of twins was not elevated in our data, yet we observed 3 cases of triplets. Some authors have suggested a cause and effect relationship between multiple births and malformations. Morison believes that there exists a vital competition between twins at a very early embryonic stage (chorio frondosum). One consequence of this competition may be lack of nutrition in one of the twins, which, if severe, may lead to a papyraceous fetus or if less severe, to an anomaly in development. The fact that we have not observed concordance in MZ twins suggests that if genetic factors are important, the vital competition is the "triggering" mechanism. Otherwise stated, if genetic factors and vital competition are essential to the formation of an anomaly of the heart, then one would expect MZ twins to be more often discordant than concordant.

Evidence from domestic animal experimentation suggests that situations similar to those described by Sawin and co-workers (1947, 1949) in rabbits may exist in man. The frequency with which kyphoscoliosis and chest deformities are observed among the propositi (10% of cases) would support this view. Lerner's (1954) and Landauer's (1952) findings in sporadic malformations in poultry have also their counterpart in our findings of sporadic distribution, high consanguinity rate, and high familial incidence in CHD.

To explain all our findings, one must assume that the genetic factors are complex and not specific. These factors would presumably influence embryonic growth by acting upon the "growth areas" described by Sawin and Edmonds in rabbit embryos. The nature of the resulting malformation would be a function of environmental conditions and the neighboring "growth areas."

D. Conclusions.—The importance of the various possible etiological factors for each of the clinical groups may be crudely weighed. In Fallot's tetralogy, genetic factors appear less important than non-genetic factors since consanguinity and familial incidence are both low, and irregularities of pregnancy, etc., are common occurrences. In pulmonary stenosis, however, genetic factors appear more important because of the high consanguinity rate and high familial incidence, and the low frequency of irregularities during pregnancy, etc. In patent ductus arteriosus, genetic factors appear somewhat less important since there is neither a marked increase in consanguinity, nor familial incidence, and abnormalities during pregnancy are relatively common. In I.V. septal defect, non-genetic factors appear to be the paramount cause of the defect. In atrial septal defect, genetic and non-genetic factors appear equally important. No judgment can be made with regard to coarctation of the aorta because of the paucity of data.

The frequency of associated malformations in the propositi does not alter these

TABLE 14. RELATIVE IMPORTANCE (INDICATED BY NUMBER OF + SIGNS) OF GENETIC AND NON-GENETIC FACTORS IN THE ETIOLOGY OF THE FIVE MOST COMMON CLINICAL SUBGROUPS

(Groups VII and VIII are not included because of their lack of homogeneity; Group VI is not included because of the small number of cases.) See text for further explanation.

Clinical subgroups	Genetic Factors		Non-genetic Factors	Frequency of associated malformations
	Consanguinity	Incidence of CHD in the sibships	Abnormalities during pregnancy	
Fallot's tetralogy	+	+	++++	++
Pulmonary valvular stenosis	++++	++++	+	++
Patent ductus arteriosus	++	++	++++	++
I.V. septal defect	+	+	++++	++
Atrial septal defect	+++	++	+++	++++

judgments since in the first four groups, where genetic and non-genetic factors vary appreciably in relative importance, the frequency of associated defect is unchanged. This might be interpreted as meaning that the associated defect is frequently merely a secondary developmental phenomenon. These observations are summarized in Table 14.

SUMMARY

The families of 1,188 propositi with congenital heart disease (CHD) diagnosed in the Hopital des Enfants Malades, Paris, France, were compared with the families of a control group of 660 children randomly selected.

1. In the entire CHD group, the sex-ratio was not significantly different from a theoretical 1:1 sex-ratio nor from that observed in the control group. But the sex-ratio was not uniform in all clinical subgroups. In patent ductus arteriosus the frequency of females was significantly higher than that of males (on the average 3:1). The frequency of males is higher than females in valvular aortic stenosis (7:1, 16 cases). In moderate truncular pulmonary atresia, the frequency of affected females is higher (9:1, 10 cases).

2. The mean maternal age for the CHD group, in its entirety, did not differ significantly from that for the control group (28.39 vs. 28.84 years). Mean birth rank is significantly higher ($t = 2.92$) in the CHD group than in the control group (2.23 vs. 2.03).

3. The average coefficient of relationship of the parents of the propositi was 3.6 times higher in the CHD group than in the control group. Considerable variation in the average coefficient of relationship was observed in the different clinical subgroups. Further evidence suggested that consanguinity increases the frequency of all malformations and, as a consequence, the frequency of CHD.

4. The frequency of infection, threats of miscarriage and premature delivery, and other abnormalities during pregnancy, was twice as high in the CHD group as in the control. Threats of interruption of pregnancy are twice as frequent among mothers under 35 years of age giving birth to children with CHD as among mothers over 35 years with similarly affected infants.

5. The frequency of CHD among the siblings of the propositi (1.46 per cent) was higher than that observed in the control group or in the general population. It was, however, not that expected for a single-gene hypothesis. In familial cases of CHD, the clinical type of heart disease is frequently dissimilar in the propositus and the affected relative.

6. Eighteen per cent of the propositi exhibited a second congenital malformation.

7. The frequency of multiple births among the propositi born with CHD was not different from that observed in the control group. All seven pairs of MZ twins showed discordance with regard to CHD, while one out of nine pairs of DZ twins showed concordance.

8. These results suggest that both genetic and non-genetic factors play a part in the etiology of CHD. The relative importance of genetic and non-genetic factors appears to vary substantially from one clinical subgroup to another.

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