Institut für Humangenetik der Universität, Göttingen

Twin Studies in Congenital Heart Diseases *

G. Jörgensen

Uchida and Rowe (1957), Lamy et al (1957), as well as Campbell (1961), were of the opinion that genetic factors do not play an important role in the genesis of congenital heart deformities. These authors could not find any concordantly affected pair among a total of 32 MZ twin pairs. Impressive family case reports and systematic investigations (Fuhrmann, 1970; Jörgensen, 1970) do not support this assumption. The results of twin investigations by Nora et al (1967) also contradict previous results. Among a total of 37 twin pairs these authors found 6/13 MZ and 1/24 DZ concordantly affected pairs.

Our own investigations began in autumn, 1966 and were recently completed. With the help of the registrar of birth offices and the cardiological team of the University of Göttingen (Prof. Dr. A. J. Beuren, Prof. Dr. H.-E. Hoffmeister, Prof. Dr. J. Koncz, Prof. Dr. J. Stoermer), we were able to find 50 index patients, each being a member of a twin pair, among 2427 propositi with different congenital heart defects.

Our own results are shown in Tab. I: 4/21 MZ (19.0 $\pm$ 8.6%) and 1/24 DZ (4.2 $\pm$ 4.1%) are concordantly affected. In five cases, the zygosity of the twins, as well as the diagnosis of respective cotwins, (stillborn or perinatal-dead) is unknown.

Tab. I. Series of randomly ascertained twins with congenital heart diseases

Authors	N.	MZ twins				DZ twins			
		N.	Concordant		Discordant	N.	Concordant		Discordant
			N.	%			N.	%	
Uchida and Rowe, 1957	26	13			13	13			13
Lamy et al, 1957	16	7			7	9	1		8
Campbell, 1961	16	12			12	4			4
Nora et al, 1967	37	13	6		7	24	1		23
Jörgensen, 1969 (present study)	45	21	4		17	24	1		23
Totals	140	66	10	15.2 $\pm$ 4.4	56	74	3	4.1 $\pm$ 2.3	71

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Combining our own results with those of literature series (Tab. I), there are 10/66 MZ (15.2 ± 4.4%) and 3/74 DZ (4.1 ± 2.3%) concordant pairs with congenital heart defects.

Tab. II shows that the specific type of heart defect is almost the same in 19/19 MZ, and only in 2/5 DZ concordant twin pairs.

In Tables III and IV twin results are differentiated according to the special morphological type of heart defect. Tab. III concerns our own investigations, and Tab. IV summarizes them with those of the literature. Sufficient randomly ascertained cases from smaller twin series of literature were added to the previously mentioned larger series (Tab. I).

A summary of the special types is necessary in order to determine if and how far the different morphological types are also heterogeneous from a genetic point of view. The highly intrapair concordance referring to special heart defect (Tab. II) is an important indication of this.

Tab. V summarizes the heart results of six twin pairs with concordant thalidomide embryopathy (Jörgensen et al, 1970). It is remarkable that none of them is concordant in heart defect.

What deductions can be made from the present examinations of twins with congenital heart diseases?

Our own investigations show that the degree of concordance in MZ twins is not as low as earlier investigations would indicate. Presumably, a part of the concordant pairs could not be found, as a result of abortion or stillbirth of both twins. In cases where a twin was stillborn or died perinatally, it is probable that this twin had a heart defect. Summarizing our own investigations with those of the literature, one may assume that approximately 15-20% of the MZ and about 4% of the DZ twins are concordant. This concordance, approximately four times higher in MZ than DZ twins, is a clear sign of cooperation of genetic influences on the genesis of congenital heart defects, and allows one to assume a multifactorial genetic inheritance.

The relatively low concordance of MZ twins could not necessarily mean that genetic influences do not play an important role in the genesis of congenital heart diseases. This relatively low concordance is probably caused by the peculiarities of twin pregnancy as such. The real influence of genetic factors should be considerably higher. Small differences of the intrauterine environment could be the cause of high discordance rates among MZ twins. In cases of the same genetical disposition, the more unfavourable intrauterine development of one member of a twin pair gives the last impulse for the genesis of the defect. The cotwin, however, remains healthy, due to the better developmental possibilities. What are the causes of these different factors of development?

DZ twins all have a dichorial placenta, whereas 65-85% of MZ twins have a monochorial one (Benirschke, 1965; Corney et al, 1968). It is remarkable that, in this type of placenta, anastomosis of the vessels appear frequently. These anastomoses lead to strong haemodynamic disturbances and to unbalances in the supply of oxygen

Tab. II. Concordant twin pairs in the series of randomly ascertained twins with congenital heart diseases

Authors	Clinical findings	
	Twin A *	Twin B *
	MZ TWINS	
McAleese, 1952	Patent ductus arteriosus	Patent ductus arteriosus
Holman et al, 1953	Patent ductus arteriosus	Patent ductus arteriosus
Ross, 1959	Patent ductus arteriosus	Patent ductus arteriosus
Nora et al, 1967	Patent ductus arteriosus	Patent ductus arteriosus
Jörgensen, 1969 (present study)	Valvular aortic stenosis	Endocarditis of aortic and mitral valves
Jörgensen, 1969 (present study)	Supravalvular aortic stenosis (" simple " type)	Supravalvular aortic stenosis (" simple " type)
Nora et al, 1967	Pulmonary stenosis	Pulmonary stenosis
Jörgensen, 1969 (present study)	Valvular pulmonary stenosis	Valvular pulmonary stenosis
Nora et al, 1967	Atrial septal defect	Atrial septal defect; Patent ductus arteriosus; Coarctation of the aorta
Nora et al, 1967	Atrial septal defect	Atrial septal defect; Ventricular septal defect
Ross, 1959	Ventricular septal defect	Atrial septal defect
Ehlers and Engle, 1961	Ventricular septal defect	Ventricular septal defect
Gedda et al, 1961	Ventricular septal defect a. v. block	Ventricular septal defect a. v. block
Gedda et al, 1961	Ventricular septal defect	Ventricular septal defect
Gedda et al, 1961	Ventricular septal defect	Ventricular septal defect
Nora et al, 1967	Ventricular defect	Ventricular defect
Jörgensen, 1969 (present study)	Ventricular septal defect	Congenital heart defect (Ventricular septal defect?)
Steinlein, 1952	Tetralogy of Fallot	Tetralogy of Fallot
Nora et al, 1967	Tetralogy of Fallot	Tetralogy of Fallot
	DZ TWINS	
Nora et al, 1967	Patent ductus arteriosus	Patent ductus arteriosus
Zoethout et al, 1964	Valvular aortic stenosis	Patent ductus arteriosus; Pulmonary stenosis; Mitral insufficiency
Jörgensen, 1969 (present study)	Valvular aortic stenosis	Congenital mitral insufficiency
Lamy et al, 1957	Pulmonary stenosis	Pulmonary stenosis
Gedda et al, 1961	Tetralogy of Fallot	Congenital cardiomegaly

* The indication " twin A " and " twin B " does not refer to birth rank.

Tab. III. Congenital heart diseases in twins (own investigations)

Congenital heart disease	N.	MZ twins		DZ twins		Twins with doubtful zygosity and doubtful conc./disc.
		Conc.	Disc.	Conc.	Disc.	
Patent ductus arteriosus	5		3		2	
Valvular aortic stenosis	7	1		1	4	1
Supravalvular aortic stenosis (" simple " type)	2	1			1	
Supravalvular aortic stenosis (" complicated " type)	1					1
Subvalvular aortic stenosis	1		1			
Functional obstructive subvalvular aortic stenosis (irregular hypertrophic cardiomyopathy)	1				1	
Coarctation of the aorta	2		1		1	
Hypoplasia of the aorta	1				1	
Valvular pulmonary stenosis	9	1	3		4	1
Atrial septal defect	5		1		3	1
Ventricular septal defect	8	1	4		3	
Eisenmenger's complex	1		1			
Morbus Ebstein	1					1
Trilogy of Fallot	2		1		1	
Tetralogy of Fallot	4		2		2	
Totals	50	4	17	1	23	5

Tab. IV. Bibliographical survey (including the present study) of congenital heart diseases in random twins

Congenital heart disease	N.	MZ twins		DZ twins	
		Conc.	Disc.	Conc.	Disc.
Patent ductus arteriosus	19	4	7	1	7
Valvular aortic stenosis	13	1	1	2	9
Supravalvular aortic stenosis (" simple " type)	2	1			1
Coarctation of the aorta	11		3		8
Valvular pulmonary stenosis	24	2	9	1	12
Atrial septal defect	17	3	6		8
Ventricular septal defect	32	7*	12		13
Tetralogy of Fallot	20	2	8	1	9

* One case also listed under " Atrial septal defect ".

Tab. V. Twins with concordant thalidomide-embryopathy and cardiac defects (own investigations)

Zygosity	Twin A	Twin B
DZ		Tetralogy of Fallot; Agenesis of ductus arteriosus
DZ		Cardiac defect
ZU		Cardiac defect
ZU	Infundibular aortic stenosis; Agenesis of aorta descendens; Ventricular septal defect	
ZU	Tetralogy of Fallot; Patent foramen ovale	
ZU		Cardiac defect (Ventricular septal defect?)

to both twins. As a result of this dissimilar placental permeation of blood, the differences in birth weight, the discordant genesis of anomalies of the organic systems, as well as defects like cleft lip and palate, heart defects, and so on, can well be explained. Corresponding anastomosis of placental vessels, in opposition to those of the MZ twins, is very rare and therefore meaningless for DZ twins' intrauterine development. This difference in the placental blood supply between MZ and DZ twins creates environmental conditions and calls in question the general statements of the classical twin method for the judgement of intrauterine developmental disturbances. The consequence is that there is an overestimation, as well as an undervaluation, of the exogenous influences concerning MZ twins.

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Prof. Dr. G. Jörgensen, Institut für Humangenetik der Universität, Nikolausberger Weg 23, 34 Göttingen, Germany.