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Thalidomide-Embryopathy in Twins

A collaborative study

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In the discussion of the thalidomide problem, the examinations of twins up to now have found little consideration, although the method of twin investigation is by far the most suitable to decidedly solve this problem. The reason for this may be that a randomly ascertained collection of an adequate series of twins is difficult to obtain.

The number of thalidomide cases in Germany amounts to approximately 5000. There are estimations which lie lower and higher than this number. Therefore a systematic statistical collection is definitely of some importance. We have found, through collection of published cases as well as through intensive inquiries, a total of 44 well documented German twin pairs as well as 5 further foreign pairs, i.e., a total of 49 cases available for a correct analysis of the problem. Eleven further pairs could not be fully analysed because of incomplete documentation. In addition, 10 further German twin pairs with " facial thalidomide syndrome " have been found. Their documentation is not yet complete; however, these cases should be included, when considering the frequency of thalidomide twins. Assuming a frequency of 5000 thalidomide cases, approximately 90% of expected thalidomide twin births have been ascertained. Among the 49 twin pairs, 6 MZ pairs are concordant and 1 discordant. Among the 26 DZ pairs, 21 are concordant and 5 discordant. Among the 16 twins with doubtful zygosity (ZU), 15 are concordant and 1 discordant.

In addition to the 49 cases, there are 11 with incomplete documentation which are included in the total analysis. This amounts to the following distribution: 9/10 MZ twin pairs are concordant; 22/27 DZ twin pairs are concordant; 21/23 ZU twin pairs are concordant. Tab. II shows the distribution in percent. It is very remarkable that both among well documented (N = 49) and total cases (N = 60), high concordance is found in MZ as well as in DZ twins. This high concordance (over 80%) of DZ is almost as high as that of MZ twins.

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Tab. I. Twins with thalidomide-embryopathy

	MZ			DZ			ZU		
	N.	Conc.	Disc.	N.	Conc.	Disc.	N.	Conc.	Disc.
Present study (N = 44)	7	6	1	22	17	5	15	14	1
Foreign cases (N = 5)				4	4		1	1	
Totals (N = 49)	7	6	1	26	21	5	16	15	1

Tab. II. Twins with thalidomide-embryopathy

	N.	Concordance %			Totals
		MZ	DZ	ZU	
Well documented cases	49	86 ± 13.1	81 ± 10.9	94 ± 5.9	86 ± 4.9
Totals	60	90 ± 9.5	81 ± 7.6	91 ± 8.4	87 ± 4.3

This clearly shows that exogenous factors are more important than inheritance in the causation of the deformities. In fact, a clear influence of genetic factors is not demonstrated by this material. Family investigations have also failed to show any genetic influence on the malformations. It is interesting that among 21 younger siblings of the affected twins which were born after the thalidomide era there are no deformities (Tab. III).

Although the concordance among MZ and DZ twins is almost the same, the intrapair difference in the degree of the defects is greater among DZ than among MZ twins.

Tab. III. Siblings (N=80) of the twins with thalidomide-embryopathy (N = 49)

Twins	Elder siblings			Younger siblings, nonaffected	Totals	Elder half-siblings, nonaffected
	Nonaffected	Died early nonaffected	Stillborn			
Present study (N = 44)	45	1	3	19	68	5
Foreign cases (N = 5)	4		1	2	7	
Totals (N = 49)	49	1	4	21	75	5

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The type of deformities in MZ twins is very similar. The degree of the defect in case 5 is homologous and in the other cases minimally different. In case 2 the younger twin has a megacolon, while the elder does not show this defect. The colon anomaly probably explains the difference in size between both twins (MZ I: 118 cm; MZ II: 110 cm). In case 4 both twins have a congenital megacolon.

Among the 21 concordant DZ twins the degree of the defect is also quite similar (N = = 15). Only in case 17 there is a great difference. However, among at least 13 concordant cases the degree of the defect is stronger in one of the twins and only in a few cases slightly different.

The greater intrapair differences among DZ twins may be explained in two different ways: (1) specific genetic factors may influence the deformity; (2) the greater quantitative discordance is in speed of development.

Even complete discordance, but also quantitatively different defects may be explained in a similar way, if slight differences in the time of the sensitive phases in organogenesis are assumed. For example, the discordance in case 33 — triphalangy in one DZ twin only — is easily explained in this way: it is probable that triphalangies develop only through damage at the end of the sensitive phase. The discordance in case 7 — " facial thalidomide syndrome " in only one of MZ twins — could also be explained in this way: the typically facial thalidomide syndrome might arise at the beginning of the sensitive phase.

In over 70% of the cases intake of thalidomide in early pregnancy has been well documented (Tab. IV).

Tab. IV. Intake of thalidomide in the early pregnancy with the twins; cases which have been proved, cases which have not been proved

	N. of twins	Unproved cases	
		N.	%
Present study	44	10	22.7
Foreign cases	5	4	
Totals	49	14	28.6

Other causative factors could not be established in our twin investigations. Paternal age is not higher than the mean in the general population, while maternal age is half a year higher than the mean control. Such an increase of the mean maternal age is not surprising as elder mothers are more likely to take sleeping pills. Furthermore, elder mothers give more frequently birth to DZ twins than younger mothers.

It is interesting that the children of higher social levels are more frequently affected than those of the lower levels. This may be due to the greater intake of drugs, or to

Tab. V. Observations of twins with reduction-deformities of extremities outside the thalidomide-era

Author	Zygosity[a]	Concordance (+) or discordance (—)	Family cases	Distinction of the deformities			
				Twin A[b]		Twin B[b]	
				One side	Both sides	One side	Both sides
Duvernoy, 1734	DZ	+			+		+
Nikoladony, 1886	DZ	+		+		+	
Timmer, 1896	DZ	—		+			
Lotheissen, 1899	DZ	—			+		
Klaussner, 1900	ZU	—		+			
Bötticher, 1904	ZU	—	+		+		
Kindl, 1907	DZ	—			+		
Renvall, 1908	ZU	—	+		+		
Hiromoto, 1913	ZU	—	+		+		
Harrison, 1919	MZ	—		+			
Löwy, 1921	ZU	+			+	+	
Ollerenshaw, 1925	MZ	+				+	
Vonnegut, 1926	ZU	—	+	+			
Orel, 1932	OS	+			+	+(?)	
Nitsche and Armknecht (case 13), 1933	MZ	—		+			
Nitsche and Armknecht (case 14), 1933	MZ	—		+			
Forbes, 1938	MZ[c]	—		+			
Goldenberg, 1948	MZ	+			+		+
Birch-Jensen (case 136), 1949	DZ	—			+		
Birch-Jensen (case 199) 1949	OS	—			+		
Schildwächter, 1953	DZ	—		+			
Dodson, 1956	OS	—	+		+		
v. Meel, 1957	ZU	—		+			
Gruber, 1958	MZ[c]	—			+		
Neel, 1958	OS	—			+		
Ring, 1959	ZU	—		+			
Severi and Dardi, 1961	DZ	—		+			
Hepp, 1962	OS	—		+			
Thomas, 1962	DZ	—					
Rössle, 1963	MZ	—		+			
Wildervanck, 1963	DZ	+			+		+
Grebe, 1964	MZ	—			+		
Hamilton, 1967	MZ	+			+		+

[a] MZ = monozygotic; DZ = dizygotic; ZU = doubtful zygosity; OS = opposite-sexed.
[b] The indication twin A and twin B does not necessarily correspond to birth rank.
[c] Thoracopagous conjoined twins.

more complete ascertainment. Other deformities, e.g., cleft lip and cleft palate, appear more frequently in the lower social levels.

Twins with reduction deformities of the extremities have also been found before the thalidomide era. Most of the extremity defects are both morphologically and etiologically different. It is important that among the total 33 twin pairs with non-thalidomide deformities of the limbs (Tab. V) only 8 pairs are concordant. Furthermore, symmetric relationships are noticeable. The deformities among pairs which were born outside of the thalidomide era concern more frequently only one side than both sides, while in thalidomide-embryopathies both sides are concerned.

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