Acta Genet Med Gemellol 30:167-187 (1981)
The Mendel Institute/Alan R. Liss, Inc.

Received 6 December 1980
Accepted 22 August 1981

On the Distribution of Nonrighthandedness Among Twins and Their Families

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In 773 three-generation families of twins, individual probability of nonrighthandedness (NRH) depends significantly on the handedness of that individual's parents. The parents of twins are much more often NRH than are their nontwinbearing siblings. The twins and their siblings apparently inherit the excess liability for NRH shown by their parents. Monozygotic (MZ) pairs are significantly about twice as often concordant (casewise) for handedness as dizygotic (DZ) pairs. Overall, the best-fitting mode of transmission is autosomal, NRH dominant to RH with penetrance of about 50% in the heterozygote, or multifactorial, with heritability of 60–70%. Under the major-gene approach, heterogeneity seems likely, with about one-third of the families showing no NRH outside of the twin sibships. MZ/DZ concordance ratio is about four in those families, suggestive of recessive inheritance. A 1.16-fold excess of NRH in twins compared to their siblings, and a 1.8-fold excess in the second-born members of same-sex discordant pairs, leaves open the possibility that a minor portion of NRH in twins may be secondary to transient hypoxia and/or acidosis.

Key words: Handedness, Laterality, Cerebral dominance, Cell differentiation, Embryogenesis, Behavior, Twins

INTRODUCTION

Lefthandedness in and of itself is of no major consequence in most of modern Western society. However, it remains of interest as the simplest indicator of membership in a particularly intriguing human minority. Among that minority, structural and functional organization of the brain differs in a variety of ways from that found in the brains of the majority.

The members of that minority are over-represented among psychotics, epileptics, alcoholics, children with learning disabilities, dyslexics, dysphasics, in both

Abbreviations: NRH, nonrighthanded ("lefthanded" plus "ambidextrous"); MZ, monozygotic; DZ, dizygotic; FOT, father of twins; MOT, mother of twins; MGF or MGM, maternal grandfather or grandmother; PGF or PGM, paternal grandfather or grandmother; GP, grandparent; ??, handedness unknown; s.s., same sex; FH +, FH −, family history of NRH positive, negative; P(NRH), probability of being NRH.

tails of I.Q. distributions, in institutions for those unable to participate productively in society, and in institutions of higher learning.

One very distinctive feature of that minority as a group, which should be suggested by the range of niches they occupy disproportionately, is a considerable enhancement of variability and what might best be called flexibility of brain development and function compared to the majority as a group [36, 39; see also Fig. 1]. Lefthanders, for example, are more likely to lose speech function as a result of brain injury, regardless of its location. But, given aphasia as a result of brain injury, a lefthander is more likely to recover, and this latter affect extends even to righthanded relatives of lefthanders. This is reviewed effectively elsewhere [40–42].

Although the expression of handedness itself is subject to social influences that still vary greatly over cultures, it is quite significantly related to numerous asymmetries of structure and function, in the brain and elsewhere, that are prenatal in origin and not plausibly subject to social pressure. Over a broad and active literature, various manifestations of the functional asymmetry of the human brain can be found to be related to every "specifically human" function of the brain and essentially every unusual development thereof [17, 25, 27, 29].

Therefore, the factors contributing to membership in that minority whose brains are built differently and who are most simply detected by lefthandedness, and the transmission of those factors, remain as sources of fundamental questions for all of human behavorial genetics. From the literature to date, it would seem that individual probability of lefthandedness is a function of relatedness to lefthanders, but that its transmission is not in any obvious or simple way Mendelian.

The most widely discussed recent models for the genetics of lefthandedness are those of Levy and Nagylaki [31] and Annett [3]. The former is a relatively straightforward two-locus model, with one locus determining the lateralization of speech capacity and the second deciding contralateral versus ipsilateral control of the fine motor sequencing basic to hand (writing) skill. The Annett model posits a single gene pair, a dominant allele of which, present in the majority, directs the installation of speech mechanisms in the left hemisphere and biases a continuous distribution of motor skill about two standard deviations in favor of the right hand. In the absence of the dominant allele, lateralization of speech capacity is hypothesized to be random, and mean difference in hand skill zero. In usual genetic terminology, then, this model has right-brain speech as a recessive trait with 50% penetrance. Lefthandedness appears primarily as an expression of the recessive genotype and in smaller part as a threshold phenomenon among those possessing the dominant allele.

Both models fit certain data under certain assumptions. Neither incorporates the significant male excess frequency of lefthandedness observed in most samples. Neither incorporates the difference in frequency of lefthanded offspring from RH $\times$ LH matings as a function of the sex of the LH parent [23, 38]. Annett [1, pp 352–353] mentions, only in passing, that this pair of facts suggests a transmission like that of pyloric stenosis (polygenic). Levy [32] attacks the literature concerning the latter observation as inconsistent. (Neither of these effects is always observed, but each is seen more often than not.)

The Levy and Nagylaki model cannot accommodate typical twin handedness data at all, but dismisses it as being due to the effects of "birth-stress" and "mir-

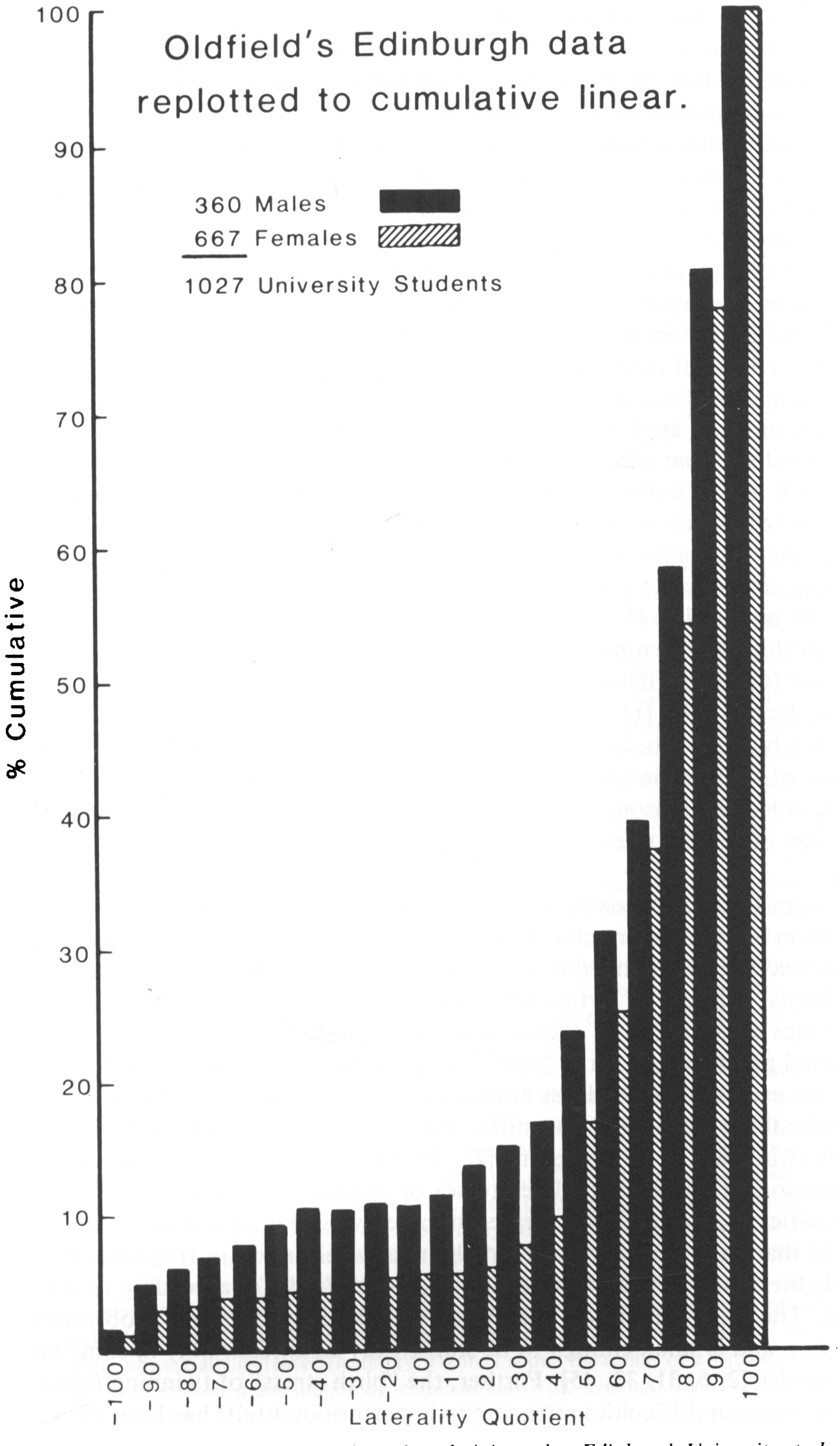

Fig. 1. *Scores on ten-item handedness questionnaire administered to Edinburgh University students [36]. Taken from semilogarithmic plot as published and replotted to cumulative linear scale. Laterality Quotient = (R − L)/(R + L), items marked + for preferred hand, ++ for very strong preference.*

https://doi.org/10.1017/S0001566000007649 Published online by Cambridge University Press

ror-imaging." Annett professes that her model can take twin data into account, but only by virtue of a large change in its major parameter. This accommodation is achieved by halving the degree of rightward bias in hand skill provided by the dominant right-shift allele, for both zygosity groups [2]. No mechanism that might justify that assumption is put forward, but it does allow for the reported 50–100% increases in frequency of lefthandedness (in both zygosities) relative to singletons, and correctly predicts the MZ-DZ concordance ratio for lefthandedness at about 2.

Collins [16] typifies the use of twin data to argue that handedness has no genetic basis. He argues forcefully against the usual approach of invoking birth stress and mirror-imaging as a means to dismiss the inconsistency of twin data with the results of other approaches. Since he is convinced that that block of results cannot be discarded in this standard way, Collins goes on to insist that it must be applied, applies it at face value, and thereby discards instead all of the other evidence that can be interpreted to support a genetic determination of handedness. It was in a discussion of this paper by Collins that I set out the argument that the twin study method requires the fundamental assumption that both twin zygosity groups share with each other and with the singleton majority (to which we hope to apply the results of such analyses) the same origin and development of the trait in question [7, 19]. Since this seems to be untrue for lefthandedness, for relationships between handedness and various parameters of schizophrenic illness [6], and for overall developmental integration of growth in the head region as reflected by the teeth [11, 12], there are adequate reasons for considering the classic twin-study approach, as applied to date in handedness research, inappropriate for studies of the genetic contributions to human brain function asymmetry development. Adequate reason, yes; satisfying, no; any such approach obviously begs the question of at least one extra determinant of handedness specially related to twinning.

Except for the approach represented by Collins, it is standard operating procedure in handling twin data on handedness to invoke "birth stress" as the source of the excess of lefthandedness among twins. This concept places twins among firstborns, high-parity births, retardates, alcoholics, and epileptics, for example, as groups associated with excess frequency of lefthandedness on the one hand and reported pregnancy or birth "stress" on the other [5]. Its application as an explanation for excess lefthandedness among twins is consistent with the existence of a considerable excess of various difficulties in pregnancy, birth, and the first year of life in twins relative to singletons [28, 30, 34, 35]. It fails in its turn, however, to accommodate differences related to sex or zygosity. The relative increases of birth difficulties are substantially greater in male twins than in females, and far greater in MZ than in DZ twins. However, the relative elevation in frequency of lefthandedness among twins has not been reported to differ according to sex of the twins. The excess reportedly associated with monozygosity is not observed in all samples, and is small enough to be statistically significant only in some large pooled samples [2, 6, 31, 33, 45]. Further, the "birth stress" of twinning (specifically as to the common difficulties attending twin parturition itself) has been shown to be a phenomenon virtually proper to the secondborn twin [18]. No effect of birth order within the pair upon the frequency of lefthandedness had been shown until very recently [14], when it was found that lefthandedness was concentrated over five-fold in the *firstborn* members of 52 handedness-discordant MZ pairs, with no effect in DZ's.

The development of my arguments concerning "birth stress," "mirror-imaging," handedness, and twinning may be followed through several previous papers [6–12]. This paper will report the results of a study of the distribution of nonright-handedness in a large sample of twin families.

MATERIALS AND METHODS

Questionnaire data concerning, among other things, handedness of family members were collected in 1975–1977 from about 800 families with twin children, with the eager and competent assistance of the National Organization of Mothers of Twins Clubs. In final form, this represents usable handedness information on about 10,000 people in 773 three-generation families.

The questionnaire concerned, in addition to handedness: the use of alcohol, tobacco, and eyeglasses; difficulties with speech, reading, writing, and spelling; epilepsy; nervous, mental, and emotional problems; employment; education; and the distribution of sexes of family members. Approximately half of the sample arrived in packets representing the whole memberships of various clubs. There is no reason to suppose that the sample is selected for families with any particular interest in nonrighthandedness.

Zygosity was determined on the basis of questions similar to those used by Cohen et al [15] in their zygosity-diagnosis questionnaire. I have not cross-validated this set of questions with blood typing, but with few exceptions each answer fell into one of two easily-distinguished patterns. Higher multiples, and multiple multiples, were few in number, and the questionnaire was poorly designed for their responses; these for the most part have not been usable. By our classification, this sample consists of: 197 MZ male, 198 MZ female, 109 DZ male, 101 DZ female, and 166 DZ female-male pairs.

The questionnaire instructed that handedness was to be classified as "right, ambidextrous, or primarily left" for the twins and their parents, and right versus lefthanded or ambidextrous for sibs, grandparents, aunts, and uncles of the twins. Left and ambidextrous have been pooled in most analyses (a practice I will explain and test below). No criteria for these definitions were specified. The operative criterion is therefore the presence of a departure from full righthandedness sufficient to have drawn a social distinction; in other words, the "social definition."

"Lefthanders," however defined, up to and including strict lefthandedness, have usually been found to be a rather more variable group than righthanders. "Ambidexterity" in casual American English is generally taken to include any significant departure from full righthandedness short of full lefthandedness. This is characteristic of a large fraction of the people who would call themselves lefthanded given righthanded as the only alternative. The use of this category reduces the need for forced choices, and allows us to observe the effect of variation in the criteria at least to the extent of comparing (strong lefthandedness versus all else) against (strong righthandedness versus all else).

Although Satz and his colleagues [39] interpret their data to indicate that self-report of "lefthandedness" is unreliable, those data in fact show that self-report agreed with assignment by ten-item questionnaire with 93% overall accuracy, using a cutoff of zero difference between hands, or 95% using the best cutoff, at an index of $+2$ on their scale of ± 10 difference between hands. Overall accuracy was 89% using their composite of all tests at its apparent best cutoff, -0.13 z. (The composite was their unweighted average of the standardized $(R - L)/(R + L)$ score on each test; no use was made of any differences among the tests in discriminating power, or of any differences in relationships, such as within-group covariances, among the test scores.) Self-report of "righthandedness" agreed 93% with the results of their testing, and such individuals were with rare exception superior with their right hands on all tests. Self-reported "lefthanders" were best described as highly variable in the results of testing; some were "strictly" lefthanded, a few nearly as righthanded as the "righthanders," but most were intermediate, indicating substantially increased flexibility. Figure 1 shows the results of a separate study [36] that supports this view, showing a distribution of semiquantitative (20-item questionnaire) laterality that indicates the population to be composed of a fairly strictly righthanded majority and a highly variable nonrighthanded minority. In short, there seems to be no simpler or more reliable criterion for membership in the unusually-lateralized minority than self- or parental-report.

Some statistical notations used here which may not be universally familiar are: $\chi^2_n = \chi^2$ with n degrees of freedom; $\hat{o}$ = sample odds ratio. In comparing two proportions a/b versus c/d, $\hat{o}$ = ad/bc.

This is provided as a measure of association the relative strength of which among two or more comparisons is easily appreciated for quick comparison. It directly represents the relative probability of the outcome as a function of the presence of the antecedent factor in question. This information is not provided by the χ^2 value, which is a function of both level of association and sample number [24].

RESULTS

Representativeness of the Sample and General Findings

As a first test of the applicability of this dataset, the gross frequencies over various subgroups of family members were compared with published values from other studies. The results show a frequency of nonrighthandedness among the second-degree relatives of the twins identical with that in the general population of adults (Table 1), according to the most recent review known to me, and slightly less than that in the largest and most recent singleborn sample included in that review [45]. The frequency of nonrighthandedness among the twins in this sample, over three years of age (Table 2), does not differ significantly from the frequency assessed by self-report in a sample of 399 school-age twin pairs recruited from complete lists of twin pairs in Philadelphia schools [13]. The frequency in the corresponding age range of this sample (Fig. 2) is practically identical to theirs. I take these results together to indicate the absence of significant ascertainment bias relative to overall frequency of nonrighthandedness.

A consistent increase in frequency of nonrighthandedness from one generation to the next (Table 2) agrees with findings in all of the two-generation studies reviewed by Annett [1, 2].

Also consistent with most other studies, the frequency of nonrighthandedness is greater overall among males than females (Table 2).

The frequency of nonrighthandedness in twins does not differ significantly from that in their siblings. There is no difference due to zygosity among the twins, and no difference due to sex among the twins or their siblings (Table 2).

Parents of Twins

The parents of the twins, in both zygosities, show a very clear excess of nonrighthandedness relative to their own same-sex siblings, or to all other members of their sex in the parental generation (Table 3a, b).

The Twins

Figure 2 shows that the distribution of hand preference classification is sensitive to age, as might be expected. Through the third year of life, many twins are reported as of "unknown" handedness, and *ambi* appears to be an indeterminate transition classification. Beyond that point, the classification frequencies are relatively stable, and in good agreement with previously reported values assessed by self-report [13]. Table 4 shows the effect of minimum age cutoff on casewise concordance. In MZ's, concordance declines steadily with age until three years. In DZ's, this decline continues until five years. This might be taken to indicate that MZ's are more concordant than DZ's not only in ultimate hand preference, but also in the developmental establishment of that preference. In both zygosities, three years is the division across which the difference in concordance rates is maximized. In almost all of the analyses presented here, I have used this division.

TABLE 1. General Population Frequency of Nonrighthandedness

Five singleton studies	
Reviewed in [43]	1297 LH/15212 = 0.085
This study	
All second-degree relatives	556 LH/6585 = 0.0844

TABLE 2. Distribution of Nonrighthandedness in Twin Families, Excluding All Unknowns

Relationship	LH or Ambi/Total	
Grandfathers	103/1359	(0.076)
Grandmothers	104/1358	(0.077)
Grandparents	207/2717	(0.076)
Aunts	129/1855	(0.070)
Uncles	220/2013	(0.109)
Aunts and uncles	349/3868	(0.090)
Fathers	135/769	(0.175)
Mothers	101/768	(0.132)
Parents	236/1536	(0.152)
Male twins (s.s.) over 3 years old	59/286	(0.206)
Female twins (s.s.) over 3 years old	56/264	(0.212)
MZ twins over 3 years old	71/348	(0.204)
DZ twins over 3 years old	76/352	(0.216)
All twins over 3 years old	147/700	(0.210)
Brothers over 3 years old	78/433	(0.180)
Sisters over 3 years old	69/380	(0.182)
Siblings over 3 years old	147/813	(0.181)

Analyses presented in Tables 5 and 6 address the issue of concordance as a function of zygosity. Table 5 shows the counts and percentages for each pairwise and individual classification, with *ambi* as a separate class. Table 6a shows the pairwise expansion in three classifications based on the individual frequencies from Table 5, and the zygosity-specific goodness-of-fit to the predicted random pairwise assortments. With three of the six pairwise classes having expectations below 5, these particular χ^2 values should be considered of comparative value only.In both zygosities all matched-pair classes are overrepresented and all discordant classes underrepresented compared to random expectations. The departure from random pairing is much greater for MZ's than for DZ's.

Reducing the question of matching to a dichotomy (matched versus unmatched), only MZ's depart significantly from random pairing, using either R versus (A or L) (Table 6b) or (R or A) versus L (Table 6c).

Comparing MZ and DZ concordance rates for the minority trait only (the usual twin study approach), Table 7 shows that MZ pairs are significantly more often concordant for nonrighthandedness using either the three-part classification

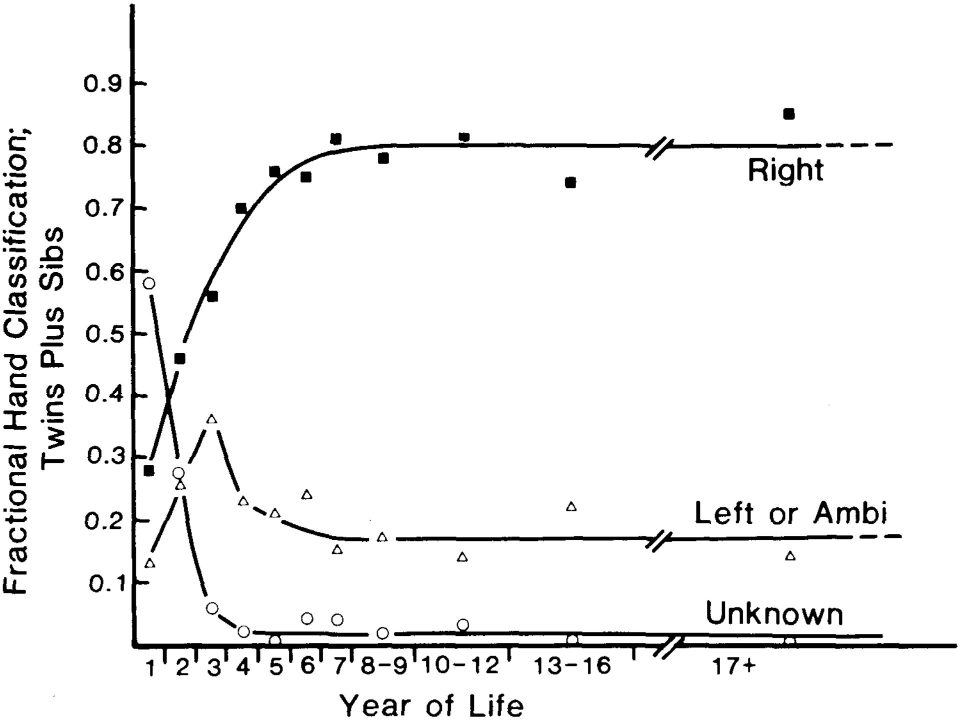

Fig. 2. Fraction of twins and sibs with the indicated hand preference classifications in each age or age group. Twins pooled over sex and zygosity. Age-grouping was done arbitrarily to provide comparable sample sizes at ages between 7 and 20. Numbers of twins in the successive groups are: 194, 238, 242, 162, 150, 122, 146, 132, 138, and 26.

TABLE 3a. Excess Nonrighthandedness Among Parents of Twins, I. Compared to Their Own Same-Sex Siblings

Fathers of MZ twins	67 LH/397	(0.169)	χ^2_1 = 10.60; $\hat{o}$ = 1.83
MZ paternal uncles	43 LH/465	(0.092)	
Mothers of MZ twins	51 LH/397	(0.128)	χ^2_1 = 4.93; $\hat{o}$ = 1.60
MZ maternal aunts	38 LH/473	(0.080)	
Fathers of DZ twins	68 LH/376	(0.181)	χ^2_1 = 8.46; $\hat{o}$ = 1.66
DZ paternal uncles	52 LH/478	(0.109)	
Mothers of DZ twins	50 LH/376	(0.133)	χ^2_1 = 7.62; $\hat{o}$ = 1.80
DZ maternal aunts	35 LH/476	(0.074)	

TABLE 3b. Excess Nonrighthandedness Among Parents of Twins, II. Compared to All Members of Their Sex in Parental Generation

Fathers of MZ twins 67 LH/397 (0.169)	All MZ uncles 113 LH/1038 (0.109)	χ^2_1 = 9.39; $\hat{o}$ = 1.55
Mothers of MZ twins 51 LH/397 (0.128)	All MZ aunts 69 LH/958 (0.072)	χ^2_1 = 11.08; $\hat{o}$ = 1.78
Fathers of DZ twins 68 LH/376 (0.181)	All DZ uncles 103 LH/961 (0.107)	χ^2_1 = 13.15; $\hat{o}$ = 1.69
Mothers of DZ twins 50 LH/376 (0.133)	All DZ aunts 60 LH/894 (0.067)	χ^2_1 = 14.51; $\hat{o}$ = 1.98

TABLE 4. *Casewise Concordance as Function of Minimum Age Cutoff*

	Age group										
	All	1 +	2 +	3 +	4 +	5 +	6 +	7 +	8 +	9 +	10 +
MZ pairs											
	130/195 (0.667)	116/181 (0.641)	92/147 (0.626)	48/93 (0.516)	40/71 (0.563)	26/51 (0.510)	18/33 (0.545)	14/27 (0.518)	12/21 (0.571)	12/19 (0.632)	8/14 (0.571)
χ^2 of change in concordance*		4.47	18.13	5.36							
DZ pairs											
	70/166 (0.422)	66/160 (0.412)	46/126 (0.365)	26/95 (0.274)	18/76 (0.237)	14/64 (0.219)	12/49 (0.245)	12/40 (0.300)	10/35 (0.286)	10/28 (0.357)	10/25 (0.400)
χ^2 of change in concordance*		6.87	19.95	19.63	17.59	8.9	3.20				

*Casewise concordance among pairs above and below the respective age cutoffs compared by χ^2.

https://doi.org/10.1017/S0001566000007649 Published online by Cambridge University Press

TABLE 5. Twin Concordance by Hand-Preference Classification (All Pairs 3+ Years of Age)

Pairwise classification†	MZ pairs N pairs (%)	DZ pairs N pairs (%)
RR	145 (66.5)	132 (60.6)
AA	10 (4.6)	5 (2.3)
LL	11 (5.0)	8 (3.7)
AL	3 (1.4)	0
AR	13 (6.0)	23 (10.5)
LR	32 (14.7)	46 (21.1)
??	4 (1.8)	4 (1.8)
Total	218 (214)*	218 (214)*
p(L)	0.131 (0.133)*	0.142 (0.145)*
p(A)	0.083 (0.085)*	0.076 (0.077)*
p(R)	0.768 (0.782)*	0.764 (0.778)*

†R = right, A = ambi, L = left, ? = unknown.
*Excluding unknowns (??).

TABLE 6. Test of Independence of Hand-Preference Classifications as a Function of Zygosity and Criterion (Twin Pairs Over 3 Years of Age)

6a. $[p(L) + p(A) + p(R)] = 1$ (three-way classification)

$= p^2(L) + 2p(L)p(A) + p^2(A) + 2p(A)p(R) + p^2(R) + 2p(L)p(R)$

		(LL)	(LA)	(AA)	(AR)	(RR)	(RL)
MZ:	Expected	3.78	4.72	1.5	28.4	131	44.5
	Observed	11	3	10	13	145	32
	$(O - E)^2/E$	13.79	0.627	48.17	8.35	1.496	3.51
	$\chi^2_3 = 75.94$, $p \ll 0.0005$*						
DZ:	Expected	4.50	4.78	1.27	25.18	129.5	48.28
	Observed	8	0	5	23.	132	46
	$(O - E)^2/E$	2.72	4.78	10.96	0.189	0.122	0.108
	$\chi^2_3 = 18.80$; $p < 0.005$*						

6b. $[P(L \text{ or } A) + P(R)] = 1$ (two-way classification, ambi = left)

		(R, R)	(R, L or A)	(L or A, L or A)	
MZ:	Expected	131	73	10	
	Observed	145	45	24	
	$(O - E)^2/E$	1.5	10.74	19.6	$\chi^2_1 = 31.84$†
DZ:	Expected	129.5	74	10.5	
	Observed	132	69	13	
	$(O - E)^2/E$	0.048	0.338	0.595	$\chi^2_1 = 0.981$†

6c. $[P(L) + P(R \text{ or } A)] = 1$ (two-way classification, ambi = right)

		(R or A, R or A)	(R or A, L)	(L, L)	
MZ:	Expected	161	49	11	
	Observed	168	35	4	
	$(O - E)^2/E$	0.304	4.0	12.25	$\chi^2_1 = 16.55$†
DZ:	Expected	156	53	4.5	
	Observed	160	46	8	
	$(O - E)^2/E$	0.103	0.925	2.722	$\chi^2_1 = 3.75$†

*D.f. = 6(classes) − 2(estimated parameters: $p(L) + p(A) + p(R) = 1$) − 1.
†D.f. = 3(classes) − 1(estimated parameter: $p(L \text{ or } A) + p(R) = p(L) + p(R \text{ or } A) = 1$) − 1.

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TABLE 7. Concordance Comparison as a Function of Criterion (Twin Pairs Over 3 Years of Age)

	Concordant pairs	Discordant pairs	Casewise concordance for nonrighthandedness	
7a. (p(L) + p(A) + p(R)) = 1 (three-way classification)				
	LL, AA	RL, RA, LA		
MZ	21	48	0.467	$\chi_1^2 = 7.40$
DZ	13	69	0.274	
7b. (p(L or A) + p(R)) = 1 (two-way, A = L)				
	LL, LA, AA	RL, RA		
MZ	24	45	0.516	$\chi_1^2 = 12.48$
DZ	13	69	0.274	
7c. (p(L) + p(R or A)) = 1 (two-way, A = R)				
	LL	LR, LA		
MZ	11	35	0.386	$\chi_1^2 = 2.24$
DZ	8	46	0.258	

(Table 7a) or R versus A-or-L (Table 7b), but *not* by the use of R-or-A versus L (Table 7c).

Parent-Child Relationships

Table 8 shows results of mating-type analyses conducted on the two levels of nuclear families available from these data. In the breeding of the parental generation from the grandparents, each lefthanded parent raises the probability of lefthanded children by a factor of about 1.6. In the breeding of the twin generation, a similar increase (1.5 ×) is observed in the presence of one lefthanded parent, but numbers are too small to justify comment as to the effect of a second lefthanded parent.

Table 9 shows that twin pair concordance for nonrighthandedness bears a direct, but not statistically significant, relationship with parental handedness, in both zygosities. Table 9b extends this question to the history of nonrighthandedness throughout the first and second degree relatives, with a similar result.

Table 10 puts this question the other way around and shows the distribution of nonrighthandedness in the various classes of relatives tabulated according to zygosity and concordance. With some exceptions, these results seem to indicate more nonrighthandedness in relatives of concordant NRH twin pairs, in both zygosities. In DZ's only, the frequencies over all relatives of discordant pairs seem to be intermediate between those of RR and LL pairs, but this is true in only 5 of the 12 separate classes of relatives.

Gender Effects in the Distribution of Nonrighthandedness

In these data, as in most previous studies, there is a highly significant excess P(NRH) among males versus females, overall. It is possible with these data to analyze for the existence of sex-dependent transmission, by comparing mother-son, father-son, mother-daughter, and father-daughter transmission. Overall, the results of these analyses are negative; there is no consistent evidence or pattern of

TABLE 8a. Mating Analysis: The Breeding of the Parental Generation

Matings by handedness	No. families	Left or ambi/total progeny (p(L))
GM × GF		
R × R	1153	414/3964 (0.104)
R × L	87	44/271 (0.162)
L × R	84	53/319 (0.166)
L × L	15	12/42 (0.286)

See footnote to Table 8b.

TABLE 8b. Mating Analysis: The Breeding of the Twin Sibships (No Age Restriction; Unknowns Excluded)

MOT × FOT	No. families	Twins only	Sibs only	Twins and sibs
R × R	545	227/942 (0.241)	109/634 (0.172)	336/1576 (0.213)
R × L	119	72/204 (0.353)	20/112 (0.179)	92/316 (0.291)
L × R	85	55/140 (0.393)	32/117 (0.274)	87/257 (0.339)
L × L	16	6/24 (0.250)	7/17 (0.412)	13/41 (0.319)

All individuals of unknown handedness are excluded from the count. R = righthanded, L = left-handed or ambidexterous. p(L) consistently greater in L × R than in R × L matings, but never significant. (L × R) + (R × L) matings, pooled, versus (R × R): χ^2_1 = 18.54 for parental generation, 20.76 for twins only, 3.37 for sibs only, 19.71 for twins plus sibs. (L × L) versus pooled (L × R) + (R × L): 4.04 for parental generation, nonsignificant in the twin generation.

TABLE 9a. Casewise Concordance for Nonrighthandedness as a Function of Parental Handedness (Twin Pairs Over 3 Years of Age)

Parental mating	R × R	R × L	L × R	L × L	RL + LR + LL
MZ	26/57 (0.456)	14/21 (0.667)	8/14 (0.571)	0	22/35 (0.629)
	N(families) = 158	N = 29	N = 24	N = 4	
		χ^2_1 = 2.58 (R × R versus others)			
DZ	14/58 (0.241)	4/13 (0.308)	6/16 (0.375)	2/4 (0.500)	12/33 (0.364)
	N = 148	N = 33	N = 28	N = 7	
		χ^2_1 = 1.57 (R × R versus others)			

TABLE 9b. Casewise Concordance as a Function of Family History (Twin Pairs Over 3 Years of Age)

	Positive		Negative
MZ	32/61 (0.525)		10/24 (0.417)
	N(families) = 142		N = 56
		χ^2_1 = 0.8	
DZ	20/69 (0.290)		2/18 (0.111)
	N = 157		N = 48
		χ^2_1 = 2.4	

TABLE 10. Frequencies of Nonrighthandedness in Various Classes of Relatives From Families With Twins of Known Handedness Over Three Years of Age by Zygosity and Concordance Class

	MZRR	MZRL	MZLL	DZRR	DZRL	DZLL
MGM	16/134 = 0.119	3/41 = 0.073	2/21 = 0.095	9/124 = 0.073	5/66 = 0.076	1/16 = 0.100
MGF	15/134 = 0.112	4/41 = 0.098	3/21 = 0.143	9/124 = 0.073	3/67 = 0.045	0/10
PGM	7/122 = 0.057	3/39 = 0.077	0/19	7/124 = 0.056	7/61 = 0.115	1/9 = 0.111
PGF	7/122 = 0.057	4/39 = 0.103	0/18	7/124 = 0.056	10/61 = 0.164	2/9 = 0.222
M-ANT	13/91 = 0.143	5/27 = 0.185	2/10 = 0.200	14/87 = 0.161	12/48 = 0.250	1/9 = 0.111
M-UNC	24/107 = 0.224	5/34 = 0.147	5/12 = 0.417	14/90 = 0.156	10/51 = 0.204	3/12 = 0.250
P-ANT	8/97 = 0.082	3/24 = 0.125	1/14 = 0.071	6/86 = 0.070	9/40 = 0.225	1/7 = 0.143
P-UNC	10/108 = 0.093	3/27 = 0.111	5/19 = 0.263	12/91 = 0.132	11/48 = 0.229	4/9 = 0.444
All second degree relatives	(A) 100/915 = 0.109	(B) 30/272 = 0.110	(C) 18/134 = 0.134	(D) 78/850 = 0.092	(E) 67/442 = 0.152	(F) 13.81 = 0.160
MOT	17/143 = 0.119	7/45 = 0.156	4/24 = 0.167	16/133 = 0.120	12/65 = 0.185	4/13 = 0.308
FOT	18/144 = 0.125	7/45 = 0.156	7/24 = 0.292	26/134 = 0.194	11/67 = 0.164	3/13 = 0.231
SIS	15/65 = 0.231	3/25 = 0.120	4/12 = 0.333	22/61 = 0.360	4/37 = 0.108	2/9 = 0.222
BRO	16/82 = 0.195	2/21 = 0.095	3/10 = 0.300	18/84 = 0.214	12/36 = 0.333	3/9 = 0.333
All first degree relatives	(G) 66/434 = 0.152	(H) 19/136 = 0.140	(I) 18/70 = 0.257	(J) 82/412 = 0.199	(K) 39/205 = 0.190	(L) 12/44 = 0.273
All relatives	(M) 166/1349 = 0.123	(N) 49/408 = 0.120	(O) 36/204 = 0.176	(P) 160/1262 = 0.127	(Q) 106/645 = 0.164	(R) 25/125 = 0.200

Significance tests: A versus B, n.s.; A + B versus C, $\chi_1^2 = 0.745$; D versus E, $\chi_1^2 = 10.64$; E versus F, n.s.; D versus E + F, $\chi_1^2 = 11.91$
G versus H, n.s.; G + H versus I, $\chi_1^2 = 5.39$; J versus K, n.s.; K versus L, n.s.; J versus K + L, n.s.
M versus N, n.s.; M + N versus O, $\chi_1^2 = 4.79$; P versus Q, $\chi_1^2 = 5.02$; Q versus R, n.s.; P versus Q + R, $\chi_1^2 = 7.32$.
The trend P < Q < R is significant.

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TABLE 11. The Effect of Birth Order in Twin Pairs on Handedness in Discordant (R, A or R, L) Pairs

		Birth order of NRH twin		
		First	Second	
A.	All discordant pairs over 3 years of age	47	67	z = 1.873
	All discordant pairs under 3 years of age ("unknown" pairs excluded)	19	31	z = 1.697
B.	MZ only, discordant pairs	23	38	z = 1.921
	DZ only, discordant pairs	42	59	z = 1.692
	All discordant pairs	65	97	z = 2.514, p = 0.012*
C.	Male (s.s.) only, discordant pairs	14	31	z = 2.534, p = 0.0056*
	Female (s.s.) only, discordant pairs	21	32	z = 1.54
	All same-sex discordant pairs	35	63	z = 2.828, p = 0.0047*
D.	Opposite-sex discordant pairs	30	34	z = 1.0

*Two-tailed p-values; normal-approximation test of differences in proportions from 0.5.

sex-dependent transmission. The primary source of sex difference in P(NRH) seems to be sex-dependent penetrance, but further analysis is in progress.

Possible Nongenetic Contributions

On the issue of the possible contributions of "birth stress" to any excess frequency of lefthandedness in twins, any effects of sex, zygosity, or birth order may be relevant. By reference to Table 1, as stated above, you may see that we observe no effects of sex or zygosity in twins over three years of age. We do observe an effect of birth order within pairs (Table 11). Over all handedness-discordant same-sex pairs, the *second-born twin* is 1.8 times as likely to be the lefthanded member ($\chi_1^2 = 8.0$, $p = 0.0047$). The ratio declines with age (<3 versus ≥ 3), and tends to be higher ($1.2\times$) in MZ than DZ pairs, and higher ($1.45\times$) in male than in female same-sex pairs. In opposite-sex pairs, the effect appears very small. The ratio is higher in negative-history than in positive-history families. In all subgroupings the differences are in the same direction.

If we were to remove from consideration the number of discordant pairs by which second-twin nonrighthandedness is in excess (9 MZ, 11 DZ over 3 years of age), the basic results change as follows:

	MZ, 3+	DZ, 3+	Compare to
Frequency of nonrighthandedness	0.193	0.193	Table 1
Casewise concordance for NRH	0.571(48/84)	0.309(26/84)	Table 7b

The MZ/DZ concordance ratio does not change. The frequency of NRH in twins becomes more similar to that in their siblings.

DISCUSSION

Criteria of Handedness

I believe that these results support my opinion, originally derived from the published work of others, that the division of the human population according to hand preference most naturally falls between those who are fairly strictly right-

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handed and those who are not. According to MZ/DZ concordance comparisons derived in this study, the (right versus nonright) division may well have a genetic basis; the hypothesis that (left versus nonleft) has no genetic basis cannot be rejected.

Excess Nonrighthandedness in Twins

We must address the long history of observations in the literature to the effect that twins are more likely than singletons to be lefthanded. It has been unusual at best for such studies to have derived their reported frequencies from twin and singleton samples gathered and assessed in the same study [33]. In this present study, the only available direct comparison is between the twins and their own siblings. The observed 16% excess in twins over their siblings (all over three years of age) is not statistically significant (Table 1).

Far greater, and highly significant, excesses are found in the parents of twins compared to the aunts and uncles of twins ($\hat{o} = 1.69$, $\chi_1^2 = 45.8$) and in the offspring of NRH parents compared to the offspring of RH parents ($\hat{o} = 1.78$; $\chi_1^2 = 87.6$). The parents of twins are, with few exceptions, not themselves twins. These observations, taken together, make it seem highly unlikely that any consequence of twinship per se makes any major contribution to the frequency of nonrighthandedness among twins.

We cannot produce from these data a direct comparison of frequencies between twins and an *unrelated* group of singletons similarly assessed. However, the clear dependence of individual handedness on the handedness of that individual's parents, and the clear concentration of nonrighthandedness among the parents of twins, suggests that a comparison between twins and people from all-singleton families would probably demonstrate an excess among twins.

The Genetics of Handedness

MZ twin pairs are quite significantly more likely to be concordant for handedness than are DZ pairs, except when ambidexterity is considered equivalent to righthandedness. The children of NRH parents are significantly more likely to be NRH than are the children of RH $\times$ RH matings. MZ/DZ concordance ratios change directly, but not significantly, as a function of parental handedness.

Concordance rates here are *casewise* concordance rates, calculated as

$$\frac{\text{cases in concordant pairs}}{\text{all cases}}$$

(equivalent to probandwise concordance under complete ascertainment). Under complete ascertainment, the expected DZ casewise concordance rate for a fully penetrant recessively inherited trait is 0.25; for a fully penetrant dominantly inherited trait, 0.5; exactly analogous with expected segregation in sibships. In the case of reduced penetrance due to nongenetic factors, expected MZ casewise concordance approximates the penetrance. The MZ/DZ concordance ratio is unchanged by reduction of penetrance, due to commensurate reduction in both rates.

Since the trait in question here was assessed in every member of a sample of twins collected without specific regard to that trait, we should be able to consider

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this a situation of complete ascertainment. The concordance ratio may therefore be expected to approximate two for a dominantly inherited, and four for a recessively inherited, Mendelian trait. Multifactorial inheritance theory, based on normally distributed underlying liability, also calls for an MZ/DZ concordance ratio of two for any trait that is to have the same heritability in MZ and DZ twins. (The difference between "dominant" inheritance with low heterozygote penetrance and multifactorial inheritance is subtle at best and in general primarily academic, both being basically additive.)

Using nonrighthanded (NRH) twins as probands, these results present the customary indications of dominant inheritance: MZ/DZ concordance ratio 0.516/0.274 = 1.88 ≅ 2. Frequency in sibs of NRH twins, frequency in parents of NRH twins, and DZ concordance rates are not significantly unequal. From these data, penetrance of a supposed dominant allele for NRH would be estimated at about 50% in the heterozygote.

The most readily apparent problem with this interpretation of these summary data is the observation that the frequency of NRH among second-degree relatives of NRH twins is significantly greater than one-half of that frequency in their first-degree relatives. This would also be a problem for a *uniform* recessive or multifactorial interpretation, but it seems to result primarily from the apparent increase of frequency of nonrighthandedness from each generation to the next (Table 1) [2]. This is reminiscent of "anticipation" in dominantly-inherited diseases of variable onset and severity. This phenomenon is now known to be an artifact of selection for relative health through parenthood, requiring later onset and/or milder course [see 46]. This might suggest a *reduction in fitness* associated with lefthandedness in general. This might not be surprising, in view of the variety of unusual mental development modes associated with nonrighthandedness. It might conceivably be due in some part to a secular trend of relaxing social pressure against use of the left hand.

The possibility of genetic heterogeneity is clear: in about one-third of these families, there are no NRH individuals outside of the twin sibships (Table 9b). In those negative-history families, MZ/DZ concordance ratio is nearly four, the value characteristic of recessive inheritance. In the positive-history families, that ratio is about two, characteristic of dominant inheritance. There is no significant difference in frequencies of NRH among the twins as a function of *overall* family history (0.217, positive; 0.202, negative). In the positive-history families, the frequency of NRH in twins over 3 years of age is identical to that in their parents (0.217), and very similar to that in their siblings (0.206).

The frequency of NRH in the sibs of NRH twins differs by a factor of two as a function of family history outside the twin sibships (FH−, 9/72, 0.125; FH+, 25/105, 0.238; χ^2_1 = 3.52). Although just short of conventional statistical significance, this observation would seem to lend further support to the prospect of genetic heterogeneity. In both FH+ and FH− families, DZ concordance rates are very similar to the frequencies in the sibs of NRH twins (FH+: 0.290 versus 0.238; FH−: 0.111 versus 0.125). MZ concordance rates, DZ concordance rates, and sib repeat frequencies are, in both FH+ and FH− families, close to 50% of the expected values for fully penetrant dominant and recessive genotypes, respectively. In no case do the values differ between MZ and DZ families.

Under the assumption of a normally distributed underlying liability (multifactorial model), the correlation in liability between MZ twins is 0.774; between DZ twins, 0.422. This yields an estimated heritability of about 80% (methods from [43, 44] as set forth in [20]). Sib–sib correlation in liability is 0.312, and parent-child correlation 0.262; yielding a heritability estimate in the range of 55%. Correlation with second-degree relatives is 0.173, yielding a heritability estimate of 69%. The discrepancy in results between twin and nontwin comparisons might be seen as suggesting an extra contribution to liability arising from twinship in addition to a heritable contribution segregating in the families.

Gender Effects on Handedness Distribution

Overall, these data fit the common pattern of a substantial male excess in P(NRH). This is found, however, only in the parental generation here; there is no sex difference in P(NRH) among the grandparents or in the twin sibships. Overall, there is no real indication of sex-dependent transmission. There appears, however, to be a complex pattern of nonrandom variations in the male/female P(NRH) ratio over various relationships within these families. These features will be investigated further; if a useful interpretation can be made, it will be reported in a later paper. The explanation for the excess P(NRH) associated with twinning may be there.

Possible Nongenetic Contributions to Nonrighthandedness

The use of these concordance rates for estimates of heritability is to some extent compromised by the observed effect of birth order, and perhaps also by interactions of that effect with sex and zygosity, however small, if those are real. These results leave the existence of some minor level of "pathological" lefthandedness [5, 40] as a possibility that might require further consideration. The weakness of *overall* sex and zygosity effects, if they exist at all, stands against thinking of any excess frequency of nonrighthandedness in twins as part of the complex of malformations and prenatal and perinatal risk factors associated with (primarily MZ and male) twinning [28, 30, 34, 35]. The possibility that the transient hypoxia and acidosis that so often characterize the status of the second twin at birth [18] may have some effect remains an open consideration. In simpler words, if "birth stress" contributes anything to the distribution of nonrighthandedness in twins, it appears to do so only in the moment of birth.

The extent to which nonrighthandedness is excessive in the second-born members of handedness-discordant pairs accounts for about 17.5% of all the discordant nonrighthanded twins in this sample, over 3 years of age. Assuming that a similar fraction of the members of concordant pairs had become lefthanded for the same reason, the total effect would be to account fairly closely for the observed 16% excess frequency of nonrighthandedness in twins compared to their siblings. Concordance is reduced for both zygosities, to 0.44 MZ, 0.225 DZ; the ratio 1.95, $\chi^2_1 = 8.3$. Under the dominant model, penetrance is reduced to about 45%. Under the multifactorial model, heritability becomes 61% in MZ's, 68% in DZ's, in better agreement with estimates not involving twinship.

The findings of this study with respect to the effect of birth order are in clear contrast to those of Christian et al [14]. The contrast is clear; the reasons are not.

This sample is younger, and my criteria are broader, but the direction of the effect observed here is constant throughout the age range of this sample and is unaffected by exclusion of ambidexters. Nor does the ratio vary substantially with age or with the exclusion of ambidexters.

This result can be interpreted as being consistent with difficulties known to be common in twin parturition, and some supposed consequences thereof, but the relationship between transient hypoxia and nonrighthandedness remains far short of proven casuality. Observations that the right hemisphere tends to have the larger blood flow in the majority [37] might be taken to suggest that the left hemisphere would be the more vulnerable to a transient perfusion deficit of the kind supposed to be responsible for "pathological lefthandedness" [40]. But any relationship between regional blood flow differentials and vulnerability to changes in the level of oxygenation of the blood is at best plausible and not directly demonstrable in the human. Suffice it to say that these results allow the interpretation that a minor fraction of nonrighthandedness among twins may result from subtle brain changes that might conceivably occur as a consequence of transient hypoxia.

Speculation on the Relationship Between Twinning and Symmetry Determination

The excess of NRH in the parents of twins relative to their own nontwinbearing siblings suggests that some special biological relationship exists between twinning and nonrighthandedness. The effect apparently can be exerted through either parent, whose handedness is in turn a function of the handedness of either grandparent. The relationship is the same with respect to twinning of either zygosity. This I interpret as suggesting the existence of one or more features held in common by the mechanisms originating MZ and DZ twinning. That there must also be elements unshared between the two kinds of twinning process also seems clear, if for no other reason than because they must occur at very different stages of development [10].

A relationship between MZ twinning and the embryonic determination of body and brain symmetries or asymmetries is easy enough to imagine, as witnessed by decades of literature uncritically invoking "mirror imaging." Even in the absence of any concrete idea how such a relationship might be enacted by developing cells, there remains the compelling notion that a group of cells destined to produce a single body symmetry in 99.7% of viable human embryos must somehow form two body symmetries. It is not so easy to imagine such a relationship for DZ twinning, but from these results it seems we have reason to believe that both MZ and DZ twinning processes bear some special relationship with an excess frequency of nonrighthandedness, that appears to be primarily of heritable origin. Whatever that special relationship may be, it seems to have nearly identical distribution in the families of both zygosity groups of twins, and essentially identical effect in both zygosities, with respect to handedness itself.

If that relationship has anything to do with embryonic brain symmetry or asymmetry determination, as it would seem that it must, then early DZ embryogenesis must bear some similarity to that of MZ twins. What that similarity may be is by no means immediately clear, but consider the following:

It has been demonstrated that there indeed exists a mode of human twinning in which the individual embryos may share parts (embryonic or extraembryonic) derived from a single common fertilized egg. On the other hand it is common knowledge that DZ twinning results from the fertilization of two separately released ova, and that the ensuing side-by-side embryonic processes are no different from those of singletons until uterine resources are challenged. If one becomes sufficiently curious to pursue the question, one finds the knowledge to be of a very common sort indeed. The occurrence of bilateral tubal pregnancy is the only compelling evidence that natural DZ twinning even *can* happen that way in the human.

Normal meiosis involves two consecutive extremely asymmetric cell divisions, by means of which three-fourths of the chromosome content of the primary oocyte is discarded in the polar bodies. In order for these divisions to be so asymmetric, and thus to carry away as little cytoplasm as possible, the spindle moves from the center of the oocyte to the periphery and rotates 90° in the cytoplasm to place one of its poles closely against the cell membrane [4, Fig. 63]. Failure of either or both of those movements would necessarily result in a symmetrical division.

The failure of the meiotic spindle to achieve the peripheral migration and 90° rotation in the cytoplasm required for the extremely asymmetric cell division leading to polar body abstriction is a much simpler explanation for the delivery of two gametes than is double ovulation. There seems to be very little among the known causes of increased DZ twinning rate which would be inconsistent with this mechanism. The paper by Harlap [26] shows aging of the ovum to cause an increase in twinning (primarily DZ!). Observations by Eriksson [21] and Eriksson and Fellman [22] on the effects of situations tending to decrease coital frequency would support this view.

The idea of second-polar-body twinning is not novel. It has arisen and been dismissed in the literature on several occasions. In all cases, that dismissal has been based on failure of an erroneous test. There is no reason to suppose that second-polar-body twins should be identical for maternal genetic contributions away from the centromeres; recombination in fact makes this highly unlikely. So the possibility of major contribution of polar body fertilization to DZ twinning must still be considered open [19]. Consequently, the prospect that DZ twinning might also be related to early embryogenic symmetry- or asymmetry-determining mechanisms is open as well.

Similarities between MZ and DZ families in their unusual distribution of nonrighthandedness suggest common element(s) in the causes of MZ and DZ twinning related somehow to symmetry determination. Differences between MZ and DZ twins in relationships between handedness and several parameters of schizophrenic illness [6] together with differences in embryonic timing of MZ and DZ events [10] seem to require that there be zygosity-conditioned differences in the developmental elaboration of brain function symmetry or asymmetry relationships. The nature of those similarities and differences, and the cellular means by which they take shape, will be the subject of further inquiry. The traditions of twin-study methodology are based on believing 1) that MZ and DZ twinning processes are entirely unrelated in their origins, and 2) that those differences in very early embryogenesis have negligible developmental effects. I believe that these results make both of those assumptions seem less secure.

Acknowledgments. This work could not have been accomplished without the eager and thoughtful cooperation of the National Organization of Mothers of Twins Clubs, its member clubs, and their individual members. JoAnne Mills, Des Laux, Joy Knox, and Bill Baker have provided invaluable assistance with coding and computations. Support for the work has come from the Biology Division of Kansas State University, the Genetics Curriculum of University of North Carolina School of Medicine (grant GM 00006), and the Dean of East Carolina University School of Medicine.

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