Prenatal Development of Monozygotic Twins and Concordance for Schizophrenia

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Abstract

While twin concordances for schizophrenia have been used to estimate heritability and to develop genetic models, concordances in subtypes of monozygotic (MZ) twins can also be used to investigate the influence of prenatal development in the etiology of mental illness. We used within-pair variability and mirroring of fingerprints to estimate retrospectively the placentation status of concordant and discordant MZ twins. The results indicate that concordant MZ pairs were more likely to have been monochorionic (MC) and to have shared a single placenta, whereas discordant MZ pairs appear more likely to have been dichorionic (DC) with separate placentas. Pairwise concordances for MZ twins without MC markers averaged 10.7 percent. In contrast, concordances for MZ twins with one or more MC markers averaged 60 percent. This suggests that simple MZ concordance rates may overestimate schizophrenia heritability and that prenatal development may also be important in the etiology of schizophrenia. Because MC (but not DC) twins usually share fetal blood circulation and hence are likely to share infections, these results are consistent with the hypothesis that fetal infections may be a significant etiological factor in schizophrenia.

Schizophrenia Bulletin, 21(3): 357–366, 1995.

It is well established that monozygotic (MZ) twins are more likely to be concordant for schizophrenia than dizygotic (DZ) twins. Widely reported is Gottesman's (1991) summary, based on numerous twin studies, that the probandwise concordance for schizophrenia in MZ twins is approximately 48 percent, compared to only 17 percent for DZ twins. The MZ/DZ discrepancy is also found even with the more conservative pairwise estimation of concordance. In a meta-analysis of 21 studies, Walker et al. (1991) reported MZ/DZ pairwise concordances of 25 and 7 percent, respectively. There is high concordance for schizophrenia in MZ twins even when reared apart (Gottesman and Shields 1982). Bailey and Pillard (1993) credit these findings with helping to establish a "relative iron-clad fortress" (p. 241) for schizophrenia genetics research. The specific values for the concordance rates have been used to estimate heritability (Kendler and Diehl 1993) and to construct genetic models (Cromwell 1993).

Although the high MZ concordance and the MZ/DZ differences in concordance rates are generally attributed to genetic effects, it must be pointed out that MZ and DZ pairs do not have similar prenatal development (Phillips 1993). Furthermore, the prenatal environments can be different even for the two members of a twin pair (Melnick et al. 1978; Pridjian et al. 1991; Reed et al. 1991a, 1991b; Davis and Phelps 1995).

One of the main determinants of the prenatal environment and fetal development is the placenta. Davis and Phelps (1995) proposed that variations in twins' placentation

could also account for differences in twin concordances. They discussed the protective function of the placenta and its relevance to the hypothesis proposed by others that prenatal infections may play a significant role in the etiology of schizophrenia (Torrey et al. 1988, 1994; Bracha et al. 1992; Pulver et al. 1992; Sham et al. 1992; Adams et al. 1993; Mednick et al. 1994).

In this article, we continue to explore placentation variation in twins as it relates to twin concordance for schizophrenia. First, we delineate the two major placentation or chorionic arrangements that occur in twinning and address how they may be relevant to a viral etiology of schizophrenia. Next, we present a strategy for estimating placentation retrospectively, followed by the results of applying this strategy to a sample of MZ twins with schizophrenia. Finally, we briefly discuss the implications of our findings.

Twin Placentation and Its Relevance to the Viral Hypothesis

It has long been incorrectly held that all MZ twins share a single chorion, and according to Bryan (1992), this misinformation is still found in some medical textbooks. However, approximately one-third of MZ twins and all DZ twins are dichorionic (DC), developing separate placentas and chorions, as shown in figure 1a. In the case of MZ twins, DC placentation is the result of twinning before the fourth day following conception. The remaining two-thirds of MZ twins are monochorionic (MC), as shown in figure 1b, sharing one placenta and one chorion and, only rarely, one amnion (Bulmer 1970; Sadler 1990; Bryan 1992).

Figure 1.   Dichorionic placentation (a) and monochorionic placentation (b)

a   b
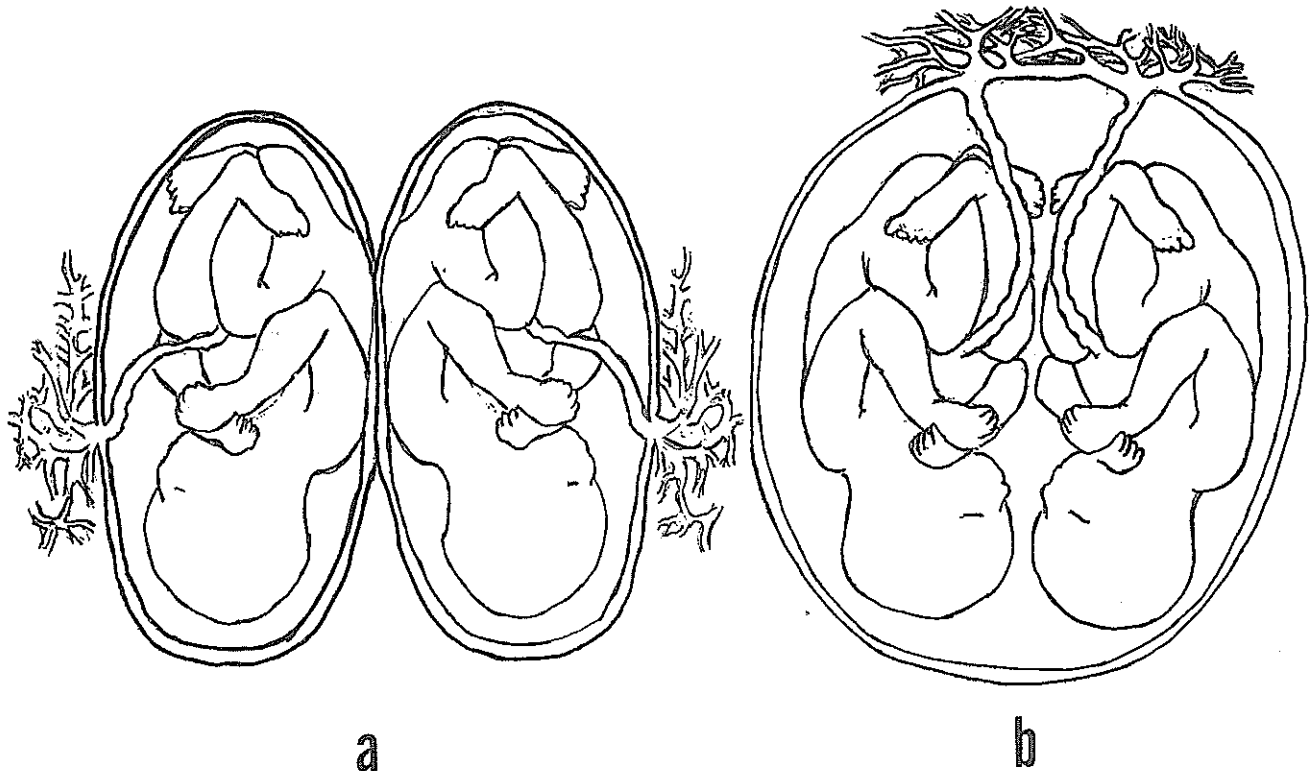
Figure 1a illustrates the separate placentas and separate fetal circulations of dichorionic twins, who can be either dizygotic or monozygotic. Figure 1b illustrates the single placenta and shared vascular communications of monochorionic placentation, which occurs only in monozygotic twins.

Perinatal mortality is more common in MC–MZ than in DC–MZ twins (Bulmer 1970), so the percentage of adult MC–MZ twins may be reduced to 55 to 60 percent of all MZ pairs (Bulmer 1970; Reed et al. 1978).

Because the placenta exerts considerable influence on prenatal health and development, there are some potentially important differences found between MC–MZ, DC–MZ, and DZ twins (Reed et al. 1978, 1991a, 1991b; Phillips 1993). One conspicuous difference between MC and DC placentation involves fetal blood circulation. Most (85%–100%) MC twins exchange blood through shared vascular communication, whereas DC twin pairs (whether MZ or DZ) very rarely exchange blood (Strong and Corney 1967; Bulmer 1970; Pezzati et al. 1993). This is relevant to the viral hypothesis because the shared vascular communication would encourage mutual infection when an infectious agent crosses the shared placenta of an MC twin pair. On the other hand, infections and other toxic insults could breach the placenta of only one twin in a DC pair, leaving the cotwin unaffected (Scerbo et al. 1986; Goedert et al. 1991). Thus, MC twins are likely to be mutually affected by such insults as bloodborne infections, while DC twins—with their separate fetal circulations—cannot share infections through an exchange of blood.

It is important to note that, in addition to creating similarities in MC twins, shared circulation can lead to some obvious differences in a subset (15%–30%) of MC twins who develop "twin transfusion syndrome" (Strong and Corney 1967). This syndrome occurs when an arteriovenous shunt between the twins creates within-pair differences in blood distribution and development. In severe cases, the donor twin may be much smaller at birth, as well as anemic (Bulmer 1970; Tan et al. 1979; Scerbo et al. 1986; Bryan 1992).

Retrospective Estimation of Placentation: A Strategy

Direct obstetrical information on placentation status in twins is not widely available. Therefore, researchers have used three retrospective markers: (1) analysis of birthweight differences (Munsinger 1977; Kamin 1978), which are suggestive of twin transfusion syndrome and therefore of MC placentation; (2) analysis of mirroring for hand preferences, which are suggestive of late twinning and therefore of MC placentation (Davis and Phelps, 1995); and (3) analysis of dermatoglyphic patterns (Reed et al. 1978, 1991a, 1991b), a technique that has been developed with samples of twins of known placentation. Each of these is discussed below.

Munsinger (1977) and Kamin (1978) used birthweight differences to investigate placentation effects on intelligence. Kamin's (1978) conclusion that MC twins were more alike on intelligence tests than were DC twins was supported by Melnick et al. (1978), who relied on a sample of twins of known placentation. Unfortunately, birthweight differences fail to correctly identify the majority of MC twins who do not suffer from chronic twin transfusion syndrome (Tan et al. 1979). Such differences provide a fairly valid but not very sensitive marker of MC placentation.

A subset of MC–MZ twins appear to mirror image for various features, including handedness, birthmarks, hair swirls, facial features, and fingerprints (Segal 1989; Lohr and Bracha 1992; Torrey et al. 1994). Mirroring is thought to occur when twinning takes place 8 or more days after conception, when MC placentation is certain (Burn and Corney 1988). Davis and Phelps (1995) used hand-preference mirroring as a marker and found that MZ twin pairs with opposite-hand preferences were concordant for psychosis in 9 of 15 cases (60%), compared with only 18 of 56 MZ pairs (32%) with same-hand preferences. However, although mirroring for handedness may be a fairly valid marker of MC placentation, it is not a very sensitive marker because it occurs in only 20 to 25 percent of MZ twins.

Fingerprints offer a third solution to retrospective investigation of twin placentation effects. Fingertip dermatoglyphic patterns are formed during the early to mid second trimester, and although they are under strong genetic influence, they are also known to be influenced by in utero events; thus, even identical twins usually do not have identical prints (Reed et al. 1978; Bracha et al. 1992; Lohr and Bracha 1992; Godfrey et al. 1993). These skin patterns can also be influenced by fetal size, nutrition, infectious agents, maternal health, and fetal growth rates, all of which have been implicated in the etiology of schizophrenia (Bracha et al. 1991, 1992; Torrey et al. 1994). Dermatoglyphic measures are more promising as retrospective markers of placentation for several reasons. First, they do not rely on relatively rare traits (i.e., large birthweight differences or left-handedness). Obviously, all twins have fingerprints, whereas

few have twin transfusion syndrome or left-hand preferences. Second, dermatoglyphic patterns, once formed in the early second trimester, do not change (as weight and perhaps handedness can), so they can provide indelible imprints of in utero events (Bracha et al. 1992). Third, and most important, their effectiveness as a retrospective marker has been confirmed in twin samples of known placentation.

The usefulness of dermatoglyphic analysis for investigating placentation effects was first demonstrated by the work of Reed et al. (1978, 1991a, 1991b). Working with 107 twin pairs of known placentation, Reed et al. (1978) identified differences, sometimes subtle, in ridge counts and skin patterns associated with placentation status. These findings were later used in samples of twins of unknown placentation to investigate prenatal influences on type A behavior characteristics (Reed et al. 1991a) and high-density lipoprotein (Reed et al. 1991b).

Although Reed's work relied on standard matching of ridge counts and fingerprint patterns and did not consider mirroring in MZ twins, it is also possible to evaluate twins' fingerprints for signs of mirror imaging (Lohr and Bracha 1992). This is also an MC marker because mirroring is well established as an effect of late twinning (Springer and Deutsch 1981; Segal 1989; Bracha et al. 1992; Bryan 1992; Lohr and Bracha 1992; Torrey et al. 1994). Comparing fingerprints for mirroring relies on the same logic outlined for using hand-preference mirroring to estimate placentation (Davis and Phelps 1995).

The purpose of the present dermatoglyphic study was to combine

standard matching and mirroring comparisons to determine if schizophrenia-concordant MZ twins have more retrospective markers of MC placentation than discordant pairs. We investigated two placentation markers reported by Reed et al. (1978): (1) total finger ridge count (TFRC), which should exhibit greater within-pair variability for MC twins; and (2) the four individual finger ridge counts (left middle finger total, the radial counts of the right and left index fingers, and the right middle radial counts), which varied significantly less for the MC than for the DC twins. We predicted that concordant twins would show greater within-pair variability for TFRC but less variability on the four individual finger ridge counts.

We also hypothesized that finger pattern and ridge count mirroring would occur more frequently in the concordant MZ twin pairs than in the discordant MZ pairs. This required comparing each finger to the cotwin's corresponding fingers on the same and the opposite hands. For example, the right index finger pattern and ridge counts of one twin would be compared with the patterns and ridge counts of the cotwin's right and left index fingers. If the fingers of the same hands matched better than the fingers of the opposing hands, it would indicate standard matching; better matches of the opposite hands would indicate mirroring. Ties indicate neither mirroring nor matching. Again, we expected more mirroring in concordant twins and more standard matching in discordant twins.

Method

Subjects. The twin panel employed for this work included 26

MZ pairs discordant for schizophrenia and 10 MZ pairs concordant for schizophrenia. Thirty-five pairs were originally recruited by the National Institute of Mental Health (NIMH) Twin Study Unit through questionnaires and literature distributed to the members of the National Alliance for the Mentally Ill and the Canadian Friends of Schizophrenics (now the Schizophrenia Society of Canada). The original project was funded by NIMH and coordinated by the Twin Study Unit, then directed by Dr. E. Fuller Torrey. The description of the project and details regarding diagnoses and determination of zygosity have been reported by Torrey et al. (1994). The data from this twin panel have involved 55 investigators acknowledged by Torrey et al. (1994). We added one pair of discordant twins to the original panel, the only pair recruited in an effort to develop a larger registry. The protocol for all measurements of zygosity and fingerprinting of this pair was the same as that used for the 35 pairs from the NIMH twin panel.[1]

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[1]The prints of one of the NIMH pairs were not included in this project because they were outliers on three of the measures. These prints were the only ones acquired through an outside agency, a local police department. The 109-percent difference in TFRC was more than 5 standard deviations (SDs) above the mean, and the pattern mirroring and standard pattern matching scores 4 and 3, respectively, were more than 3 SDs below the mean. In other words, the prints of this pair did not match well at all. In a previous report, these prints were treated as outliers because they did not alter the direction of statistical decisions (Bracha et al. 1992). Inasmuch as the prints were consis-

Fingerprint Analysis. One of the authors (H.S.B.) was involved in the original collection and analysis of the fingerprints. The dermatoglyphic data have been described elsewhere when they were used to investigate prenatal development of the twins (Bracha et al. 1991, 1992; Torrey et al. 1994). This report is the first to rely on these fingerprints as markers of placentation.

Finger ridge counts, measures, and comparisons. Following conventional procedures (Slater 1963; Lykken 1978; Bracha et al. 1992; Godfrey et al. 1993), the absolute finger ridge count (AFRC) for each finger was determined by counting the number of ridges between the center of a loop and the single triradius of a loop, or by combining the ridge counts from the center of a whorl to its two triradii. Arch patterns have no triradii, so AFRCs for arch patterns are counted as zero. The AFRCs can be compared to measure similarity, as was done in early twin studies to help determine zygosity (Slater 1963; Lykken 1978; Markow and Gottesman 1989).

The TFRC of each individual was the sum of his other 10 AFRCs. Within-twin pair differences in TFRC were expressed as a percentage of the smaller count of the two twins (Bracha et al. 1992), which helps correct for the larger differences found in male twins and in larger twin pairs in general (Lykken 1978). The four ridge counts that were

tent with three of our predictions and inconsistent with only one prediction, it seemed prudent to omit these fingerprint data, which skew the results in the predicted direction more often than not but probably do not contribute to accuracy.

expected to vary less in concordant twins were combined and represented by the percentage they contributed to the total AFRC differences for each set of twins.

Mirroring and standard matching. We used two separate methods of determining mirroring; these were based on ridge patterns (whorls, radial loops, ulnar loops, plain and tented arches) and AFRCs. For both mirroring analyses, each finger was compared to the cotwin's same finger for standard matching and to the corresponding finger on the cotwin's opposite hand for mirroring. If more finger patterns matched to the opposite fingers, the pair was classified as "mirror imaged" for patterns. If there were more matches to the same-side fingers, the pair was categorized as "standard matched." Because it is possible for an equal number of matches to occur for both kinds of matching, some twin pairs cannot be judged as mirrored or matched on this variable.

To compare ridge counts for mirroring, the AFRC on each finger was also compared to that on the corresponding fingers on the same and opposing hands to determine the best match. The differences in a pair's AFRC scores were totaled for the 10 standard and 10 mirrored comparisons. An AFRC mirroring score was created for each pair by subtracting the AFRC mirroring differences from the standard matching differences.

Because our hypotheses were clearly in one direction, we chose the one-tailed probability values for all statistical analyses. When possible, point-biserial correlations were included to express the strength of the relationship between concordance status and the dermatoglyphic variables. Point

biserial is a product-moment correlation calculated when one variable is continuous and the other is inherently dichotomous (Nunnally 1967). Planned chi-square tests were supplemented with Fisher's exact test when cell frequency dropped considerably below five, even though the chi-square distribution has been shown to render accurate conclusions even with sample sizes as small as eight (Spatz and Johnston 1989; Howell 1992).

Results

Table 1 presents the comparisons between concordant and discordant twin pairs for several dermatoglyphic variables.

Finger Ridge Count Analyses.
As seen in table 1, subset 1, TFRC varied more for the concordant than for the discordant twins. The mean within-pair differences in TFRC were 18.27 percent (SD = 19.43) for concordant twins and only 9.02 percent (SD = 7.80) for the discordant pairs (t = 2.07, df = 34, p = 0.25). The variance for within-pair differences was also greater for the concordant twins than for the discordant pairs (F = 5.96, df = 9.25, p < 0.01). The point-biserial correlation for the concordance group and the size of the within-pair differences was 0.34, p = 0.25.

In contrast, the four finger ridge counts that Reed et al. (1978) found to vary less for MC–MZ twins were found to vary less in the concordant twin pairs. As seen in table 1, subset 2, these four ridge counts accounted for 23.86 percent (SD = 10.64) of the total AFRC matching score differences in the concordant twins, and for 31.82 percent (SD = 16.05) of the

Table 1. Summary of the major dermatoglyphic comparisons of monozygotic (MZ) twins concordant and discordant for schizophrenia

Dermatoglyphic variable	Concordant twins	Discordant twins	Test statistic	Estimated value
1. Differences in TFRC:				
Mean, %	18.27	9.02	t	2.07[1]
Sample SD	19.43	7.80	F	5.96[2]
2. AFRC totals for four DC–MZ markers:				
Mean, %	23.86	31.82	t	1.73[3]
Sample SD	10.64	16.05	F	2.28 NS
3. AFRC totals for twins:				
Mirroring, % (n)	60 (6)	23 (6)	χ^2	4.43[1]
Matching, % (n)	40 (4)	77 (20)		
4. Twins with more patterns:				
Mirroring, % (n)	20 (2)	4 (1)	χ^2	4.80[1]
Matching, % (n)	20 (2)	58 (15)		
5. Total number of MC markers:				
Mean, %	1.2	0.346	t	2.75[4]
Sample SD	0.919	0.562	F	2.28[3]

Note.—TFRC = total finger ridge count; SD = standard deviation; NS = not significant; AFRC = absolute finger ridge count; DC = dichorionic; MC = monochorionic.

[1]p = 0.25.
[2]$p < 0.01$.
[3]$p < 0.05$.
[4]$p < 0.005$.

differences in the discordant twins ($t = 1.73$, $df = 34$, $p < 0.05$).

Mirror Imaging and Standard Matching of Finger Ridge Counts. Mirror imaging of finger ridge counts occurred more often in the concordant twins, while standard matching occurred more often in the discordant twins. As seen in table 2, subset 3, 6 (60%) of the 10 concordant pairs matched more fingers to the opposite hand (mirroring) than to the same hand (standard matching), whereas mirroring was found in only 6 (23%) of the 26 discordant

pairs ($\chi^2 = 4.43$, $df = 1$, $p < 0.025$). The point-biserial correlation for the number of ill twins (one or two) and their mirroring score was 0.28, $p < 0.05$.

Mirror Imaging Versus Standard Matching of Fingerprint Patterns. Six of the concordant and 10 of the discordant pairs had equal numbers of fingers that mirrored and matched for patterns, so these 16 pairs could not be included in this analysis. In table 1, subset 4, it can be seen that mirroring of finger ridge patterns was more prevalent in concordant twins,

while discordant twins were inclined to match more of their patterns in the standard comparisons with the fingers of their cotwin's same hand. Two of the three twin pairs with more pattern mirroring were concordant for schizophrenia, while 15 of the 17 pairs with more standard matches were discordant ($\chi^2 = 4.80$, $df = 1$, $p = 0.025$). Fisher's exact test yielded probability equal to 0.08.

Combined Dermatoglyphic Signs of Placentation. MC markers, including (1) within-pair TFRC differences greater than 20 percent, (2) mirroring of AFRCs, and (3) mirroring of finger ridge patterns, were totaled for each set of twins. As reported in table 1, subset 5, the mean number of MC markers for concordant twins was 1.2 per pair (SD = 0.919), compared to 0.346 per pair (SD = 0.562) for the discordant twins ($t = 2.75$, $p < 0.005$).

A summary of the results for combined MC markers by concordance status is shown in table 2.

Table 2. Number of concordant and discordant twin pairs with markers of monochorionic (MC) placentation

	Concordance for schizophrenia	
Total number of MC markers	Concordant pairs, $n = 10$ % (n)	Discordant pairs, $n = 26$ % (n)
None	20 (2)	69.2 (18)
One	50 (5)	26.9 (7)
Two	20 (2)	3.9 (1)
Three	10 (1)	0 (0)

Of the 20 pairs with no MC markers, only 2 pairs (10%) were concordant. The concordance rates rose to 50 percent for pairs with one or more markers, and rose again to 75 percent for those twins with two or more MC markers. Table 2 also shows that 80 percent (8 of the 10) of the concordant pairs had at least one MC marker, compared to only 31 percent (8 of 26) of the discordant pairs (χ^2 = 7.089, df = 1, p < 0.005). The point-biserial correlation for twin concordance and number of MC markers was 0.53 (p < 0.001).

Concordance Estimates. Four methods were used to estimate DC–MZ concordance rates. First, based on standard matching, there were only 2 (11.8%) concordant pairs among the 17 pairs who showed this DC trait. Second, based upon a median split for AFRC mirroring, only 2 (11.1%) of 18 pairs below the median for mirroring were concordant for schizophrenia. Third, of the 20 pairs who had no MC markers, only 2 pairs (10%) were concordant (see table 2). Finally, we created a subgroup of 11 pairs that had a combination of indicators of DC placentation. Because they showed both standard matching of patterns as well as no evidence of MC markers, these 11 pairs were considered more likely to be DC; among these, only 1 concordant pair was found (9.1%).

Five methods were used to estimate MC–MZ concordance rates. The pairwise concordance for schizophrenia in the 18 MZ pairs with at least one MC placentation marker was 50 percent. The concordance for pairs with two or more markers rose to 75 percent (three of four pairs). Twelve pairs showed AFRC mirroring, and six

(50%) of these were concordant. In the five pairs with TFRC differences above 20 percent, three (60%) were concordant. Of the three pairs that showed mirroring of finger ridge patterns, two (66%) were concordant.

Discussion

This report extends our earlier efforts to link concordance for schizophrenia in MZ twins with their placentation status (Davis and Phelps 1995) and prenatal development (Bracha et al. 1992). The results support the conclusion that concordance estimates in MZ twins can be refined by knowledge of placentation and that retrospective strategies for estimating placentation can be useful in twin research.

Dermatoglyphics appear to provide a fairly sensitive marker of placentation status. In general, we would expect approximately 55 to 60 percent of MZ twins to be MC (Bulmer 1970; Reed et al. 1978), and 44 percent of the MZ twins in this study were identified as having at least one MC marker. Estimates of concordance for schizophrenia averaged 60 percent in the twins displaying one or more MC markers. This estimate is consistent with our earlier study using mirrored hand preferences as a marker (Davis and Phelps 1995), in which we also reported 60 percent concordance in twins identified as MC. In contrast, concordance estimates for MZ twins with DC markers, either singly or in combination, averaged 10.7 percent. This figure is actually closer to previously reported pairwise rates of 7 and 6 percent for DZ twins than it is to reported pairwise MZ rates of 25 and 28 percent (Walker et al. 1991; Torrey 1992). Although

these refined concordance estimates are based on small samples and retrospective estimations of placentation, the results are consistent and in the hypothesized direction. They are provocative because they emerged despite the low power of the statistical tests and the limitations of retrospectively determining placentation. As Reed et al. (1991*a*, p. 16) succinctly concluded in a reference to type A behavior: "It is the subset of monochorionic MZ twins . . . which inflates the MZ correlations." We believe the same may be true of schizophrenia.

There is some evidence that twins' concordance for infectious disease is similar to that found for schizophrenia. For example, Bracha (1986) and Torrey (1992) have reported that MZ/DZ pairwise concordance rates for multiple sclerosis and tuberculosis in twins are similar to the MZ/DZ rates for schizophrenia. We can add another comparison: in twins, schizophrenia concordances (based on dermatoglyphic markers) appear similar to concordances for congenital human immunodeficiency virus (HIV) infection (based on birthweight markers). Goedert et al. (1991) reported 56-percent concordance for HIV in twins with more than 10-percent birthweight differences (a possible sign of twin transfusion syndrome and MC placentation), while those with smaller birthweight differences were only 11-percent HIV concordant.

These findings seem particularly significant given the mounting evidence for the role of prenatal infections in the etiology of schizophrenia (e.g., Torrey et al. 1988, 1994; Bracha et al. 1992; Pulver et al. 1992; Sham et al. 1992; Adams et al. 1993; Mednick et al. 1994). Because of the shared fetal circula-

tion in MC twins, the apparent higher concordance in these twins as compared to DC twins is certainly consistent with the viral hypothesis. It should be noted, however, that other interpretations are possible. Additional differences in prenatal environment due to variations in placentation, as well as additional risks associated with MC placentation itself, might contribute to brain pathology. Grafe (1993) has proposed that artery-to-artery or vein-to-vein anastomoses could create hemodynamic instability, and that these blood pressure fluctuations could lead to cerebral necrosis without requiring a bloodborne infection. Other possible confounds in MC–MZ twins could be created by fetal tissue pathology, such as rupture of the diamniotic membrane (Chen et al. 1994), placenta previa, and small placenta. Also, poorer fetal growth in general is expected in MC–MZ twins (Bulmer 1970; Phillips 1993).

Research on placentation effects in twins with schizophrenia will certainly be advanced when the best possible obstetric information regarding twins' placentas becomes available. (Several attempts to locate a panel of twins with schizophrenia and known placentation have not been successful.) Obtaining direct information on the placentation status of twin pairs with schizophrenia will require decades of patience. In the meantime, further refinement of dermatoglyphic markers of placental type would be beneficial, as would the continued exploration of other markers, such as handedness (Davis and Phelps 1995), birthweight differences (Munsinger 1977; Kamin 1978), and the mirroring of such ectodermal features as hair swirls (Torrey et al. 1994) and facial asymmetries (Lohr and

Bracha 1992). As far as we know, this study and our earlier investigation of handedness were the first to use the phenomenon of mirroring to estimate placentation, and this seems a promising strategy. In addition, using combinations of all possible available markers is recommended in future research.

Twin research has been in the forefront of efforts to understand the etiology of schizophrenia and has often been used to investigate genetic effects. However, the shortfall from 100-percent concordance in MZ twins has stimulated the search for environmental influences, and twin studies can contribute to this effort as well. It appears likely that MC–MZ, DC–MZ, and possibly DZ twin pairs are affected very differently by prenatal events and can contribute to our knowledge about such influences.

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