

Prenatal Growth Markers in Schizophrenia: A Monozygotic Co-Twin Control Study

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***Objective:** This co-twin study investigated monozygotic twins who were discordant for schizophrenia for evidence of prenatal growth differences between the affected and well co-twins. **Method:** Four dermatoglyphic markers of prenatal growth were obtained by established procedures from 26 monozygotic twin pairs discordant for schizophrenia, 13 monozygotic twin pairs concordant for schizophrenia, and several normal monozygotic twin samples. **Results:** The a-b ridge count differences between the affected and well co-twins were greater than those found for concordant and normal monozygotic pairs. In comparison with their well co-twins, the affected twins, in discordant pairs, had developed fewer epidermal ridges in the a-b interdigital area of their right palms. In contrast, no significant differences were found between the affected twins and their well co-twins on markers associated with fetal development before 13 or after 15 weeks estimated gestational age. **Conclusions:** Because the a-b ridges are known to complete development between 13 and 15 weeks estimated gestational age, the results provide physical evidence suggesting that the schizophrenia-affected monozygotic twins alone experienced a time-specific and time-limited dysgenesis during this time. Commonalities in the ontogeny of epidermal and neurological structures are discussed.*

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Several lines of schizophrenia research have investigated possible environmental influences during patients' prenatal development. For example, greater prevalence of schizophrenia in the offspring was associated with second trimester exposure to events including influenza epidemics (1), maternal grief due to death of the spouse (2), and maternal infections (3-6). Patients' obstetric problems (7, 8) and brain anomalies (9, 10) were also thought to be possible evidence of developmental problems during the second trimester.

In related work, affected and well co-twins in schizophrenia-discordant monozygotic twin pairs have been compared for possible early developmental differences (8, 10-16). These co-twin control studies employed the schizophrenia-discordant monozygotic twin pairs

panel recruited by the National Institute of Mental Health (NIMH) Twin Study Unit (14), and, with control of genotype (13, 17, 18), it was possible to demonstrate that the affected twins had more brain and neurological anomalies (8, 10, 14). However, the affected twins did not have significantly more minor physical anomalies, obstetric complications, or lower birthweights, which would have been additional evidence of developmental difficulties (14). Apparently, these last three traits are not exclusively associated with second trimester development (13, 14, 19-21).

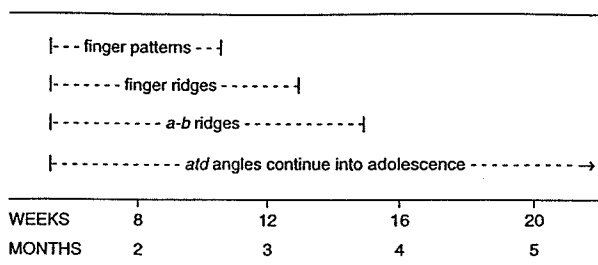
To further explore the timing of developmental difficulties, a co-twin study would especially benefit from use of selected developmental markers associated with narrow and specific prenatal periods. Several dermatoglyphic measures can provide such information about the fetal time periods most associated with schizophrenia (11, 12, 14, 21-24). Figure 1 identifies the developmental timelines and the estimated gestational ages for completion of finger patterns, finger ridge counts, a-b ridge counts, and atd angles (23, 24). Figure 2 illustrates the last two markers and the methods for assessment. These four dermatoglyphic markers are affected by fetal growth complications. For example, a higher number of finger whorl patterns were associated with prenatal infections (25-29), while greater whorl frequency variability, a-b interdigital ridge count asymmetry, and atd angle variability were associated with fetal alcohol syndrome (30-32). Other examples of dysgene-

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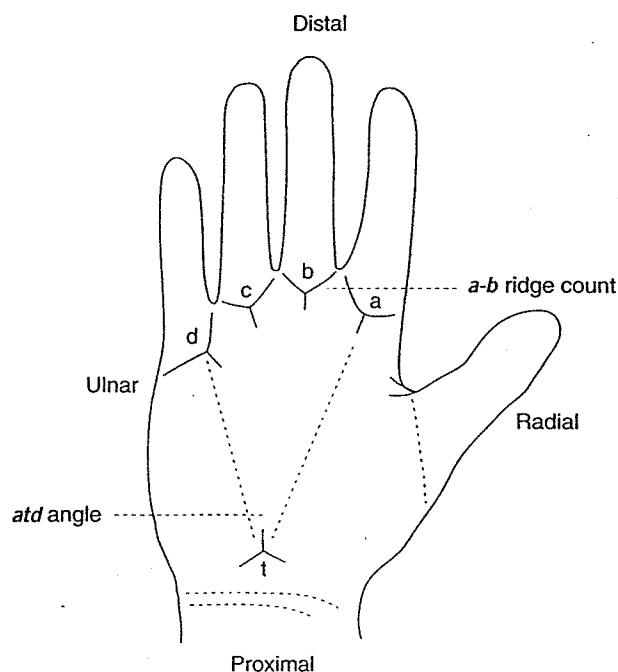
FIGURE 1. Timelines for Dermatoglyphic Markers Used to Assess Fetal Development



sis included lower *a-b* ridge counts and wider *atd* angles in subjects selected for prenatal exposure to rubella and evidence of rubella stigmata (25, 33). In addition, greater *atd* angles, *a-b* asymmetry, finger pattern asymmetries, and ridge count asymmetries were reported in dyslexia (34–36), which, like schizophrenia, has been associated with prenatal complications including viral infections (36). In summary, prenatal complications have been associated with both dermatoglyphic anomalies and greater risk of schizophrenia, as well as other conditions.

Previous studies suggest that dermatoglyphics may help identify the timing of a prenatal dysgenesis in schizophrenia. Three studies reported *a-b* ridge count asymmetry in schizophrenic patients (37–39), which would implicate the period before 15 weeks estimated gestational age. In addition, in one of the NIMH co-twin panel studies, Bracha et al. (12) found that schizophrenia-discordant monozygotic twins varied more than did seven normal monozygotic twin pairs on total finger ridge counts, which could push the time back to before 13 weeks (23, 24). However, we have found reason to question the finger ridge count effects. The normal monozygotic twins were seven pairs recruited for the NIMH twin panel, and we have become aware that these normal monozygotic twins appear to have had less than representative total finger ridge counts. Their mean total finger ridge count of 150.00 (SD=30.40) differed significantly from that reported for 400 North Americans by Schaumann and Alter (22) (mean=131.65, SD=50.95) ($t=2.16$, $df=414$, $p<0.02$, two-tailed). In contrast, the total finger ridge counts of the schizophrenia-discordant monozygotic twins were more typical (mean=135.70, SD=51.72) ($t=1.07$, $df=461$, $p=0.14$, two-tailed). We have calculated a very high intraclass correlation for the schizophrenia-discordant monozygotic twins ($r_1=0.98$) on the basis of the published data (12). It follows logically that the schizophrenia-discordant monozygotic twins' total finger ridge count could not be considered less typical than would be expected with normal development. This realization caused us to seek larger, published normal twin samples for new comparisons and caused our interest to focus on the *a-b* interdigital ridge count because of the previous findings of *a-b* asymmetry mentioned earlier in this article (37–39). In the absence of finger ridge

FIGURE 2. Methods for Assessing *a-b* Ridge Counts and *atd* Angles From the Palm of the Hand



count anomalies, *a-b* ridge count anomalies would support a second trimester timing of developmental divergence. We hypothesized that the co-twin control study method could evaluate such dermatoglyphic differences within schizophrenia-discordant monozygotic twins.

METHOD

For the present study, we took advantage of the extensive literature about epidermal ridge development to employ the four dermatoglyphic markers in figure 1 as “chronomarkers.” To investigate the development of schizophrenia-discordant monozygotic twins affected by schizophrenia, we returned to the NIMH twin panel of monozygotic twins (14). Co-twin comparisons provided control of genotype (13, 17, 40), while schizophrenia-concordant monozygotic twins, normal monozygotic twins, and nontwins allowed additional comparisons.

Subjects

The NIMH twin panel included 26 pairs of schizophrenia-discordant monozygotic twins (11 female and 15 male), who had been discordant at least 5 years (mean=14.0) at the time of testing. The panel also included 13 schizophrenia-concordant monozygotic pairs (three female and 10 male), in whom the co-twins were diagnosed as schizophrenic, or, in three cases, as schizotypal with histories of hallucinations or antipsychotic medication, and seven control pairs of normal monozygotic twins (four female and three male). These 46 monozygotic pairs were originally recruited for a large multidimensional study organized by the Twin Studies Unit at NIMH. After complete description of the study to the subjects, written informed consent was obtained (14).

This panel of twins has been exhaustively studied and described elsewhere (8, 10–16). After being recruited through the newsletters of the National Alliance for the Mentally Ill and the Schizophrenia Society of Canada (formerly Canadian Friends of Schizophrenics), the twins traveled to Washington, D.C., for 4 or 5 days of testing. Zygosity

TABLE 1. Correlation of Dermatoglyphic Prenatal Growth Markers Between Normal Monozygotic Twins and Monozygotic Twins Discordant or Concordant for Schizophrenia^a

Monozygotic Twin Group	Correlation (r_1)			
	Whorls	Absolute Finger Ridge Counts	<i>a-b</i> Ridge Counts	<i>atd</i> Angles
Normal	0.93 ^b	0.96 ^c	0.85 ^d	0.79 ^e
Schizophrenia discordant (26 twin pairs)	0.93	0.99	0.52 ^{f,g}	0.87
Schizophrenia concordant (13 twin pairs)	0.90	0.98	0.87	0.97

^aAll correlations are significantly greater than 0; $p < 0.005$, one-tailed test.

^bNIMH twin unit; seven twin pairs.

^cFrom Lykken (42); 274 twin pairs.

^dFrom Rose et al. (43); 142 twin pairs.

^eFrom Reed et al. (44) and Reed (personal communication, May 5, 1995); 527 twin pairs.

^fComparison with 142 normal monozygotic twin pairs (42): $z = 2.55$, $p < 0.005$.

^gComparison with NIMH schizophrenia-concordant twins: $z = 2.10$, $p < 0.02$.

ity was confirmed by 19 RBC antigens. Two independent diagnoses were based on the Structured Clinical Interview for DSM-III, Patient Version, Parts I and II (41), with additional information from psychiatric records, results of the Minnesota Multiphasic Personality Inventory, and interviews with treating clinicians and family members.

For this study, comparisons were also made with data from larger normal samples. These included 137 normal monozygotic twin pairs described by Lykken (42), 142 normal monozygotic twin pairs reported by Rose et al. (43), 213 monozygotic twins described by Reed et al. (44; personal communication, May 1995), 314 monozygotic twins from a study by Bogle et al. (45), and 400 normal North American individuals reported by Schaumann and Alter (22).

Dermatoglyphic Assessments

Rolled prints were obtained during the week of evaluations and were read with light magnification. Original testing protocols included only fingerprints before palm printing was added, so palm prints were not obtained from some of the twins who were tested earlier in the project, as noted in Results. The technicians collecting and scoring these prints were not informed of the diagnoses or the intended analyses. Interrater ridge count reliability was $r = 0.98$, indicating high reliability. Finger pattern judgments resulted in virtually total agreement.

Finger ridge patterns were used to investigate the period between 6 and 10.5 weeks estimated gestational age (23, 24). Whorl patterns were totaled for each subject, and their pattern symmetry was assessed by counting pattern matches on their five pairs of homologous fingers (22).

Finger ridges, including those emerging between 10.5 and 13 weeks estimated gestational age (23, 24), were included in the absolute finger ridge counts. Total finger ridge counts were also compared, although the latter excludes the smaller of the ulnar or radial ridge counts for fingers that contain a whorl pattern, which results in information loss. It is thought that the total finger ridge count expresses only the size of the pattern, while the absolute finger ridge count reflects both size and intensity and may be more sensitive to nongenetic influences (16, 22). In the absence of any significant finger pattern differences between affected and well twins, differences in their finger ridge counts would indicate that discordance likely began between 10.5 and 13 weeks estimated gestational age. Left and right absolute finger ridge counts were also compared for symmetry.

The epidermal ridges between the *a-b* triradii at the bases of the index and middle fingers (figure 2) complete development later than the finger ridges, which allowed evaluation of growth up to 15 weeks estimated gestational age (23, 24). In the absence of any differences for finger patterns or ridge counts, significant *a-b* differences in the affected schizophrenia-discordant monozygotic twins would indicate that developmental differences occurred between 13 and 15 weeks estimated gestational age.

Finally, the *atd* angle was used to measure the relationship of the length of the hand to its width. This angle is influenced by skeletal

growth, which can continue into adolescence (22). Without differences for epidermal ridges on the fingers or *a-b* interdigital area, significant *atd* differences would suggest that developmental differences occurred after 15 weeks estimated gestational age.

The four markers were compared for 1) similarity within twin pairs, 2) left- and right-hand symmetry of subjects, and 3) differences between groups of twins.

Data Analysis

Intraclass correlations (r_1) were used to assess similarity of twin pairs for the four dermatoglyphic traits. These correlations were compared by the r_1 to z transformations method (46). Group means were tested with two-tailed Student's t tests. We have set the p values for these tests at 0.01, considering the fact that we are interested in four different

dermatoglyphic markers. When repeated measures analysis of variance (ANOVA) was performed, cell means were tested with Fisher's least significant difference repeated measures ANOVA.

RESULTS

Similarity of Twin Dermatoglyphic Development in Utero

The intraclass correlations for the four dermatoglyphic chromarkers are reported for each twin group in table 1. All correlations were significantly greater than zero. Among the four markers, only the schizophrenia-discordant monozygotic intraclass correlation for *a-b* interdigital ridge counts differed from the more twin-like appearances of the normal and schizophrenia-concordant monozygotic twins, suggesting that developmental differences were occurring between 13 and 15 weeks estimated gestational age. When compared with the 142 normal monozygotic twin pairs ($r_1 = 0.85$) reported by Rose et al. (43), the schizophrenia-discordant twins' *a-b* ridge counts ($r_1 = 0.49$) were clearly less twin-like ($z = 2.82$, $p < 0.003$). The *a-b* ridge count correlation was also significantly lower ($z = 2.32$, $p < 0.01$) than for the schizophrenia-discordant ($r_1 = 0.49$, $N = 19$) than for the schizophrenia-concordant ($r_1 = 0.89$, $N = 13$) twins.

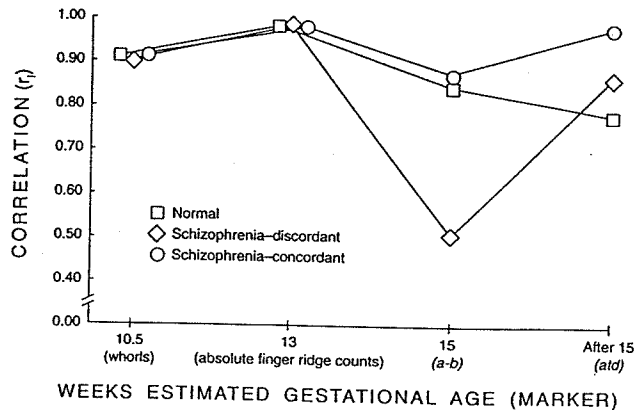
The intraclass correlations were used to create dermatoglyphic profiles that illustrate the developmental trends for all twin groups (figure 3). The most apparent decline in intrapair similarity in figure 3 can be seen in the 36% reduction in the common variance for the schizophrenia-discordant monozygotic twins' *a-b* interdigital ridge counts ($r_1 = 0.49$), when compared to the normal twins ($r_1 = 0.85$).

As planned, each dermatoglyphic variable was also assessed for within-pair differences, including symmetry, and between-twin-group differences as reported later according to estimated gestational age.

Finger Pattern Development Before 10.5 Weeks Estimated Gestational Age

No significant differences for finger tip patterns occurred between the well and affected schizophrenia-dis-

FIGURE 3. Intraclass Correlations for Dermatoglyphic Similarity of Monozygotic Twins Discordant and Concordant for Schizophrenia and Normal Monozygotic Twins



Number of twin pairs:	10.5 (whorls)	13 (absolute finger ridge counts)	15 (a-b)	After 15 (a/b)
Normal	7	136	142	527
Schizophrenia-concordant	13	13	13	9
Schizophrenia-discordant	26	26	19	12

cordant twins that might suggest that developmental differences began before 10.5 weeks estimated gestational age. Whorls for affected (mean=2.60) and well (mean=2.72) twins were not significantly different (paired $t=0.55$, $df=25$) and were comparable to the 2.62 mean whorls reported for 400 normal North American nontwins (22).

No significant trends for asymmetry of finger patterns were found. For all twin groups, the percent of homologous fingers with matching patterns fell within the normal range of 74% to 82% reported for numerous populations (22). Pattern symmetry was 80.3% for schizophrenia-discordant twins and 79.5% for the concordant twins, and the normal NIMH twins matched patterns on 81.4% of their homologous fingers. Pattern symmetry for the affected schizophrenia-discordant twins was 84.0% ($SD=16.4$), while well twins matched 76.6% ($SD=19.1$). These differences were not in a direction to suggest a developmental delay in the affected twins.

Finger Ridge Development Before 13 Weeks Estimated Gestational Age

The epidermal ridges on the finger tips that complete development by 13 weeks estimated gestational age were highly similar for the affected schizophrenia-discordant twins and their well co-twins and correlated highly ($r_1=0.99$). The mean absolute finger ridge counts of affected (mean=163.68, $SD=88.46$) and well (mean=162.36, $SD=87.38$) schizophrenia-discordant twins were nearly identical (paired $t=0.44$, $df=25$, $p=0.33$). The well schizophrenia-discordant twins had a little less symmetry of absolute finger ridge count (mean absolute left-right difference=17.89 ridges, $SD=18.68$) than the affected co-twins (mean=13.00, $SD=12.18$); however, the difference was not statistically

TABLE 2. The *a-b* Interdigital Ridge Counts for Affected and Well Co-Twins in 19 Monozygotic Pairs Discordant for Schizophrenia

Hand	Ridge Count			
	Affected Twins		Well Twins	
	Mean	SD	Mean	SD
Right	40.79	5.20	43.84	5.61
Left	43.00	3.78	43.63	3.82

significant, and it was not one to suggest a developmental delay in the affected twins (paired $t=1.24$, $df=25$, $p=0.11$).

As an additional check, the total finger ridge counts for the affected and well schizophrenia-discordant twins were compared and also found to be highly similar ($r=0.98$). The mean difference between affected twins' total finger ridge count (mean=120.81, $SD=65.79$) and well schizophrenia-discordant twins' ridge count (mean=122.50, $SD=64.72$) was extremely small (paired $t=0.161$, $df=25$, $p=0.44$).

Ridge Development Completed by 15 Weeks Estimated Gestational Age

The earliest significant dermatoglyphic differences to emerge between the affected schizophrenia-discordant twins and their well co-twins were found in the *a-b* interdigital area of the palms, which normally achieves complete development by 15 weeks estimated gestational age. The within-pair differences were greater for the schizophrenia-discordant twins (mean=7.58, $SD=4.78$) than for the schizophrenia-concordant twins (mean=3.15, $SD=1.86$) ($t=3.16$, $df=30$, $p<0.001$). The variability of the schizophrenia-discordant differences was greater as well ($F=6.58$, $df=18, 12$, $p<0.001$). At the request of a reviewer, we compared within-pair differences for female (mean=7.38, $SD=4.27$, $N=8$) and male schizophrenia-discordant twins (mean=7.73, $SD=5.31$, $N=11$); the gender differences were small and not statistically significant ($t=0.15$, $df=18$, $p=0.44$).

Table 2 shows the left and right *a-b* ridge counts for affected and well schizophrenia-discordant monozygotic twins. Asymmetry was revealed in a two-by-two repeated measures ANOVA, with diagnosis (affected versus well) by hand (left versus right). While there were no significant main effects for diagnosis ($F=3.73$, $df=1, 18$, $p=0.07$) or left versus right hand ($F=1.78$, $df=1, 18$, $p=0.20$), there was a significant diagnosis-by-hand interaction ($F=6.71$, $df=1, 18$, $p=0.02$). The interaction was created by the lower ridge count on the affected twins' right hands. The affected twins had 2.11 fewer ridges on their right than their left hands (Fisher's least significant difference $t=3.35$, $df=18$, $p=0.002$) and 3.05 fewer right-hand *a-b* ridges than their well co-twins (Fisher's least significant difference $t=4.62$, $df=18$, $p<0.0001$). The right-hand *a-b* ridge counts of the affected twins were 7% smaller than those of their well co-twins.

Within-pair differences in *a-b* symmetry were greater

for the schizophrenia-discordant twins (mean=7.63, SD=4.71, N=19) than they were for the concordant twins (mean difference=3.15, SD=1.86, N=13) ($t=3.74$, $df=30$, $p=0.0009$), or for the 314 normal twin pairs (mean difference=2.65, SD=2.44) from the work of Rose et al. (43) ($t=4.57$, $df=332$, $p<0.0003$). There was also greater variability for the schizophrenia-discordant within-pair *a-b* differences than for the concordant twins ($F=6.38$, $df=18, 12$, $p<0.005$) and the normal twins ($F=3.72$, $df=18, 313$, $p<0.005$).

Growth of the Hand After 15 Weeks Estimated Gestational Age

Relative palm lengths, as measured by the *atd* angles, indicated the affected schizophrenia-discordant twins (mean=88.25 degrees, SD=12.09) were not significantly different from their well co-twins (mean=87.08 degrees, SD=11.31) (paired $t=0.66$, $df=11$). One affected schizophrenia-discordant twin possessed *atd* asymmetry of 17 degrees, which exceeded the mean for *atd* asymmetry by more than four standard deviations. When this outlier was included in a statistical analysis, the affected twins tended to be less symmetrical (mean absolute left-right difference=4.17 degrees, SD=4.65) than their well co-twins (mean difference=1.58 degrees, SD=1.31) (paired $t=1.86$, $df=11$, $p=0.05$, two-tailed test). When the outlier was omitted from analysis, the *atd* asymmetry differences were clearly not significant ($t=0.85$, $df=10$, $p=0.21$).

On group comparisons, the schizophrenia-discordant twins' *atd* angles (mean=87.66 degrees, SD=11.47) were not significantly different from those of the concordant twins (mean=83.83 degrees, SD=11.11) ($t=0.80$, $df=20$, $p=0.22$). Even with the outlier, the within-pair differences in the *atd* angles for the discordant twins (mean=3.42, SD=4.21, N=12) were not significantly greater than those for the concordant twins (mean=2.82, SD=1.89, N=9) ($t=0.44$, $df=19$, $p<0.33$). No comparisons were made with the NIMH normal twins because *atd* data were complete for only three twin pairs.

DISCUSSION

To our knowledge, the *a-b* ridge count and *a-b* symmetry differences between affected and well schizophrenia-discordant monozygotic twins are the earliest markers of developmental differences that appear in schizophrenia-discordant monozygotic twins. These results suggest that developmental differences occurred in the period between 13 and 15 weeks estimated gestational age. Growth of schizophrenia-discordant monozygotic twins after 15 weeks appears similar for affected and well co-twins, at least as indicated by the *atd* angles; this is consistent with evidence that the twins did not differ markedly on birthweights, obstetric complications, minor physical anomalies, or several early childhood developmental traits (14). It is possible that

the skeletal hand growth of the affected twins caught up after a limited period of delay. Such a phenomenon was reported in a case of interrupted fetal bone growth during maternal viral infection (47). In addition, it may be relevant that fetal immunocompetence begins in the third trimester, although generally the capacity to produce antibodies is poor until sometime after birth (48).

Alternative explanations have also been considered. There is a possibility that *a-b* ridge development is more susceptible to the embryopathic influence than are the other dermatoglyphic markers. The *a-b* ridges do develop over a longer period of time than do the finger ridges (23, 24, 42) (figure 1). However, Martin et al. (49) reported that finger ridge symmetry is especially sensitive to environmental influence, and Penrose (50) observed that the *atd* angle is even more sensitive to environmental effects than is the *a-b* count. In addition, there is the fact that the affected twins' *a-b* reduction is not symmetrical in that it is seen on the right hand and not the left. Other asymmetrical development in the midgestation period is seen when the left cerebral hemisphere lags behind the right (51, 52). Could postmitotic mutation explain the schizophrenia-discordant monozygotic discordance for *a-b* ridges? It seems unlikely because it would require an implausibly high rate of mutation to explain the relatively high monozygotic twin concordance rate for schizophrenia (12). Finally, do schizophrenia-discordant monozygotic twins represent a special case unrelated to nontwins? Torrey et al. (14) offer much evidence that the lessons learned from the schizophrenia-discordant monozygotic twin studies will apply to nontwins.

These dermatoglyphic findings are especially interesting when considered with the neurological findings previously reported in this sample of schizophrenia-discordant monozygotic twins, which included reduced hippocampi-amygdali complexes, dilation of ventricles (10, 14), and higher neurological abnormality scores for the affected twins (13, 14). Both the neurological and the epidermal differences have been interpreted as evidence of a second trimester influence in schizophrenia (3, 6, 14, 20, 21, 29), and it is well known that they share many developmental features. Both develop from surface ectoderm (53) and experience rapid development between 12 and 16 weeks estimated gestational age (43). In addition, nerve growth factor influences the development of both the CNS (23, 54, 55) and the dermal ridges (23, 55). Moreover, nerve growth factor and epidermal growth factor are influenced by testosterone (34, 56, 57), and all three substances are present in both sexes and are functioning during dermatoglyphic development (58). Of special interest may be the putative effect of testosterone on asymmetric growth of the fetal brain, which favors the right hemisphere (59). In addition, epidermal growth factor is known to stimulate astrocyte division (60) after glia cells begin to differentiate at 12 weeks estimated gestational age (53, 61). The emerging astrocyte glia cells ultimately encircle the blood vessels serving the CNS, creating an important aspect of the blood-brain barrier (53). Finally, Roberts

(62) has interpreted the absence of gliosis in most schizophrenic patients as evidence that any early developmental injury occurred before complete glia cell differentiation. He suggests that this likely occurred during cellular migration, which would be consistent with the developmental period suggested by our findings.

The shortfall from 100% concordance in monozygotic twins creates reason to consider nongenetic influences in schizophrenia, and several authorities have suggested that environmental influences have even been underestimated (15, 16, 63, 64). Previously, we examined the placentation status of the NIMH twins to test the viral hypothesis of schizophrenia, reasoning that the shared fetal blood communications of monochorionic monozygotic twins would cause an infection in one twin to be shared directly with a co-twin (15, 16), while the separate placentas, chorions, and fetal circulations of dichorionic monozygotic twins would not. We found 60% or greater concordance for schizophrenia in those monozygotic twin pairs who possessed one or more dermatoglyphic markers of monochorionic placentation, while concordance dropped to approximately 11% in the monozygotic twins who had no such markers and appeared to be dichorionic.

The present evidence for a time-specific and time-limited embryopathy in schizophrenic patients suggests that it would be valuable to study other organs that develop in concert with the CNS and their functions and possible asymmetries in patients with schizophrenia. The neuromotor asymmetries reported by Walker and her colleagues quickly come to mind (65, 66). Such efforts might clarify the timing and nature of what may be preventable, nongenetic influences in the development of severe psychiatric disorders.

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