Second-Trimester Markers of Fetal Size in Schizophrenia: A Study of Monozygotic Twins

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Objective: *Since the second prenatal trimester is the critical period of massive neural cell migration to the cortex, and fingertip dermal cells migrate to form ridges during this same period, the authors sought to determine whether there are differences in fingertip ridge count in pairs of monozygotic twins discordant for schizophrenia, possibly indicating that a prenatal anatomical insult affected the twins differently.* *Method:* *The fingertip dermal ridges of 30 pairs of monozygotic twins (23 pairs in which the twins were discordant for schizophrenia and seven pairs in which both twins were normal) were counted by two persons trained in anthropometric research. Intrapair differences in the counts were then measured, and the differences among the pairs of normal twins were compared with the differences among the pairs discordant for schizophrenia.* *Results:* *The twins discordant for schizophrenia had significantly greater absolute intrapair differences in total finger ridge count and significantly greater percent intrapair differences than the normal twins; i.e., their fingerprints were significantly less "twin-like."* *Conclusions:* *The study suggests that various second-trimester prenatal disturbances in the epigenesis of one twin in a pair discordant for schizophrenia may be related to the fact that only one of the twins expresses his or her genetic predisposition toward schizophrenia. This is consistent with a "two-strike" etiology of schizophrenia: a genetic diathesis plus a second-trimester environmental stressor.*

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> The task ahead is to discover how genes and environment interact to produce schizophrenia. Of course, it is much easier to talk about such epigenetic interactions than to design experiments that will elucidate them! (1, p. xii)

This twin study was designed to elucidate epigenetic interactions of genes and environment in producing schizophrenia. Genes that predispose to psychosis may be expressed by making individuals more vulnerable to the disruptive effects of various commonplace prenatal insults. Recent studies indicate that many prenatal insults do not always affect both monozygotic twins to the same extent. We used the monozygotic-twin research strategy to estimate differences in environmental interference that disrupts fetal development in the second prenatal trimester. The second trimester is the critical period of massive neural cell migration to the cortex. Fingertip dermal cells also migrate to form ridges during this trimester. Differences between monozygotic twins in the anatomical dermal feature called "finger ridge count" may serve as "fossil" ("chrono-marker") evidence for any of a variety of factors that might affect one fetus differentially during the second prenatal trimester.

The study of discordant monozygotic twins is one of the most powerful methods used for sorting out the relative roles of genetic and environmental variance in medicine (2–7). For example, recent studies suggest that the monozygotic twin with chronic schizophrenia has larger ventricles and smaller temporal lobes than the nonaffected twin (4). Such important findings in schizophrenia may localize the insult in space, but not in time; that is, the brain cell loss could have occurred at any time prior to the examination.

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Given the lack of confirmation that a single major gene causes schizophrenia (2), there has been renewed interest in studies of monozygotic twins to examine the diathesis-stressor, multifactorial etiology of schizophrenia (2, 3). Unaffected twins in monozygotic twin pairs discordant for schizophrenia (one healthy twin and one schizophrenic twin) are considered to be examples of unexpressed genotypes of schizophrenia, presumably because they did not encounter a putative environmental "stressor" or "releaser" (3). The nature of the stressors or releasers has long been debated (2).

Minor facial physical anomalies (8) and minor physical asymmetries of parallel structures (9–11) are anthropometric markers found in schizophrenia that are known to reflect prenatal insult. However, the pediatric literature associates minor physical anomalies with first-trimester insults. Unlike minor physical anomalies, the embryology and genetics of the anthropometric feature known as total finger ridge count (see Method section for definition) have been thoroughly studied (12, 13). There is no such thing as an "abnormal" ridge count. However, two long-held notions—that fingertip ridge count is one of the most stable and reliable anthropometric measures and that monozygotic twins have nearly identical fingertip ridge counts—have been confirmed in recent studies. These studies show that 1) the ridge counts of monozygotic twins have an intrapair intraclass correlation of 0.96 (14)—in other words, the expected intrapair difference in ridge count between monozygotic twins approaches zero—and 2) tests of interrater reliability in ridge counting for the same individual show a correlation of 0.99 (14). Fingertip ridge counts have correlations of 0.05 and 0.49 in randomly selected individuals and first-degree relatives, respectively (5, 15, 16).

Because healthy monozygotic twins have nearly identical fingerprint ridge counts (5, 14–16), the expected intrapair difference in ridge count between two monozygotic twins free of prenatal injury approaches zero. We used this fact and a study group of monozygotic twins discordant for schizophrenia to try to localize, in time, insults to the fetal brain that may contribute to the expression of schizophrenia-related genes.

Ridge count (unlike more conventional neurodevelopmental markers such as brain ventricle size) is a permanent anatomical feature that is not permanently disrupted by postnatal insults to the subject's brain or body, such as use of psychotropic medication, drug or alcohol abuse, aging, dehydration, or trauma (12, 17–19). For this reason, ridge count remains the mainstay of person-identification techniques (19).

Ridge count has long been replaced by newer methods of determining zygosity, mainly because it is disrupted by various intrauterine insults (12, 13). The only environmental conditions that can change ridge count are intrauterine ones (12, 13, 18, 20–22). Ridge count has therefore been extensively used in recent research on prenatal injury (11, 21–23) and serves as a useful marker of deleterious intrauterine experience (18, 24). Cummins and Midlo (12) were the first to point out that "dermatoglyphics . . . are significant indicators of conditions existing several months prior to the birth of an individual . . . . Dermatoglyphics reflect the existence of differences dating from the fetal period. This freedom from the effects of later environmental influences is shared by few other traits which are accessible to investigation . . . [and] dermatoglyphics may aid in some investigations which call for reconstruction of events in the intrauterine history of an individual" (pp. 185–186).

Recent data, collected with a comprehensive National Institute of Mental Health (NIMH) prenatal history questionnaire for mothers of monozygotic twins, suggest that differences in total finger ridge count between normal monozygotic twins correlate most strongly with second-trimester deleterious events. We administered a questionnaire about deleterious events during pregnancy to a group of 30 mothers of monozygotic twins from a twin registry. We also measured the absolute intrapair differences in fingertip ridge count for each twin pair. The subscale measuring deleterious events that occurred during the second trimester in utero was the best predictor of increased intrapair differences in total finger ridge count and accounted for 36% of the variance. The next best predictor accounted for less than 2% of the variance (unpublished paper of Bracha et al.). A review of the embryological literature also indicated to us that total finger ridge count may be a specific marker for environmental insult in the second trimester of pregnancy (12, 13, 18, 21, 23, 24). Fingertip dermal cells migrate to form ridges (fingerprints) during the second prenatal trimester (13, 18). Abnormalities in fingertip ridge count have been reported in subjects with developmental brain disorders in which second-trimester systemic insults to the fetus are hypothesized to interact with genetic vulnerability (13), including the following: developmental reading disorder (22), some cases of mental retardation (23), fetal alcohol syndrome (25), and in utero viral infections (e.g., rubella and cytomegalovirus) (13, 26–28).

Studies of prenatal rubella infections clearly indicate that although the effect of the virus is paramount, the virus may be necessary *but not sufficient* to produce the clinical entity. Some genotypes cause individuals to be more sensitive than others to the neuropathogenic effects of prenatal rubella (27). Similarly, genes that predispose to schizophrenia may act by merely making individuals more vulnerable to the disruptive effects of various commonplace prenatal insults (3).

There have been several previous ridge count studies of schizophrenia. Most of them were performed before the effects of prenatal insults (e.g., rubella) were discovered and were patterned after studies of trisomy 21 (29). These studies resulted in inconclusive findings (unpublished review paper by Przybyla and Bracha). Three common flaws in the studies were 1) failure to control for genotype, 2) failure to take into account the fact that there is no such thing as an abnormal ridge count, and 3) failure to realize that since ridge count directly correlates with second-trimester fetal size (12,

13, 30), one twin's deviations from the measurements of his or her normal monozygotic twin need not always be in the same direction to be informative. Specifically, in a set of monozygotic twins, one twin's lower ridge count than that of the nonaffected twin is associated with insults which retard the physical growth of the affected fetus during the second trimester (30). Conversely, an affected monozygotic twin's having a higher ridge count than that of his or her nonaffected twin is associated with second-trimester insults that produce generalized fetal edema in the affected twin and thus make the fetal fingertip volar pads larger (13). A discrepancy in ridge count in either direction in monozygotic twins can thus be viewed as a second-trimester fetal size marker (i.e., a chrono-marker) and is the "fossilized" result of random minor, mostly unrecognized insults that caused either growth retardation or edema in the affected twin during that trimester (12, 13).

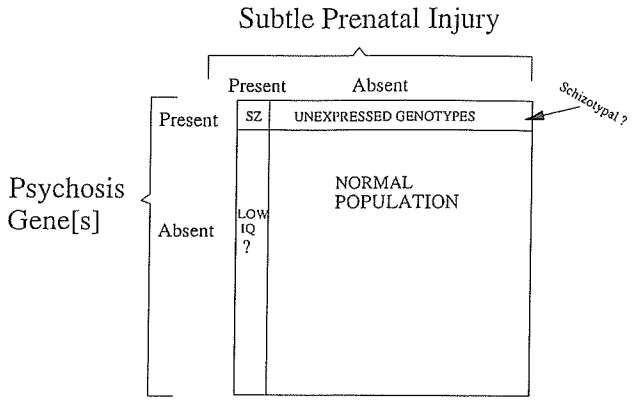
It has recently become clear that many prenatal insults, especially ischemias, frequently do not affect both monozygotic twins to the same extent (18, 31–33). In this study we fully controlled for the genetic contribution to fingertip dermal features by comparing the intrapair differences in fingertip ridge count in two groups of monozygotic twin pairs: twins discordant for schizophrenia and nonpsychotic twins. Slater's well-known sample of monozygotic twins discordant for schizophrenia (5) was far too small to allow this intrapair kind of analysis. We hypothesized that the intrapair differences in ridge count of monozygotic twins discordant for schizophrenia would be larger than those of nonpsychotic monozygotic twins.

METHOD

The study subjects were 23 pairs of twins (46 individuals) from the United States and Canada recruited over a 7-year period (1984–1990) by the Twin Studies Unit at NIMH as part of a large multidimensional study of twins discordant for schizophrenia (4). This group has been exhaustively studied and described in part elsewhere (4, 7). All of the twin pairs were monozygotic, as determined by physical similarities (by I.I.G.) and as confirmed by 19 RBC antigens.

Each individual was interviewed by two senior NIMH research neuropsychiatrists (L.B.B. and E.F.T.) with the complete Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P), parts I and II (34). The SCID videotapes were also examined by a senior clinical psychologist-geneticist (I.G.G.). All psychiatric diagnoses were made according to *DSM-III-R* criteria. Nine of the 23 pairs were female and 14 were male. Their mean age was 32.5 years (range=19–46) at the time of the analysis. The mean length of discordance was 11.2 years (range=4–24). Discordant pairs with fewer than 4 years of discordance were excluded a priori from the analysis. Belmaker et al. (6) have shown low rates of conversion to concordance beyond the 4-year period. On the basis of risk rates and data from the studies of monozygotic twins by Pollin and associates at NIMH (6), we estimate that only a few of the 23 discordant pairs are likely to become concordant.

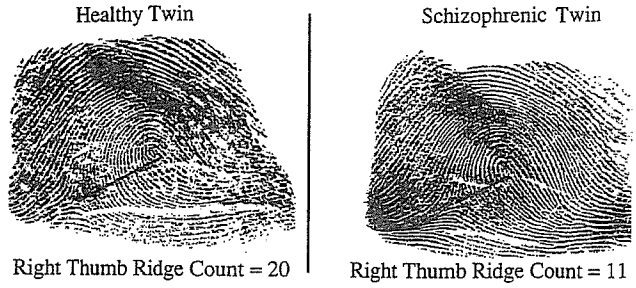
FIGURE 1. The "Two-Strike" Hypothesis of the Etiology of Schizophrenia (SZ)



Genes that predispose to schizophrenia may act by making individuals more vulnerable to the brain-disrupting effects of commonplace prenatal insults. Consequently, nonschizophrenic genotypes who suffer a second-trimester insult may manifest ridge count anomalies without manifesting schizophrenia. Therefore, by design, the study group of twins and a comparison group of normal twins should not be matched for prenatal insults or family history (4, 7). Also, by design, the only two requirements for inclusion in the comparison group in this study were no diagnosis of psychotic illness and no known history of prenatal insults according to information from the 39-item NIMH prenatal history questionnaire.

As we have mentioned, the expected intrapair difference in ridge count for monozygotic twins free of prenatal injury approaches zero (5, 14, 15, 35). We obtained the fingerprints of a comparison group of nonschizophrenic subjects consisting of seven pairs of adult monozygotic twins (14 individuals). Three of the seven pairs were male and four were female. Six of the nonschizophrenic pairs had been extensively studied and described elsewhere (4, 7). One subject in each of two of these pairs met the criteria for a single episode of major depression in full remission (*DSM-III-R* diagnosis 296.26) when administered the SCID. Four of the pairs were found to have no mental illness (*DSM-III-R* V code 71.09) according to the SCID (nonpatient version). The seventh pair of nonschizophrenic monozygotic twins (72-year-old sisters) was recruited mainly because of its high genetic loading for schizophrenia (one younger sister with chronic schizophrenia and one aunt with an early onset of psychosis). This caused the pair to be especially valuable for the study because, according to the "two-strike" hypothesis of the etiology of schizophrenia (figure 1), normal monozygotic twins who are genetically at risk but do not phenotypically express schizophrenia should not have an elevated intrapair difference in total finger ridge count. This rea-

FIGURE 2. Method Used for Total Finger Ridge Count[a]



[a]Prints are from one pair of monozygotic twins discordant for schizophrenia.

soning notwithstanding, statistical analyses demonstrated no differences between the pairs of twins discordant for schizophrenia and the normal comparison pairs in the number of prenatal insults as recorded by the NIMH prenatal history questionnaire (unpublished paper of Taylor et al.).

Using standard inking techniques, we obtained prints from each finger on both hands for all subjects (Faurot Crime Detection Equipment, Elmsford, N.Y.). The total finger ridge count analyzed in this article was from the first counting for every subject. Figure 2 shows the method used. All ridges along a straight line connecting the triradial point to the closest point of the core were counted. Ridges containing the point of the core and the triradial point were excluded. The sum of the ridge counts for all 10 fingers yielded the standard total finger ridge count for each person (9, 17, 19). The counting was done by a research assistant (S.K.) who was trained in the standard technique of dermatoglyphic ridge counting (13, 19) and who was unaware of the twins' diagnoses and pair membership.

To establish the reliability of the ridge count data, ridges of all the twins studied were also independently counted by a trained medical geneticist (B.P.). After this second counting, an intraclass correlation coefficient was computed. The resulting correlation for the two raters was 0.98, indicating a high degree of reliability of the ridge count data.

By design, family history was not an exclusion criterion for the normal comparison group, nor was prenatal insult an exclusion criterion for the twins discordant for schizophrenia. Data on twins are unique because an individual can serve as his or her twin's "built-in" comparison subject. In other words, studies of monozygotic twins allow a powerful and unique design in which the unaffected member of each pair can be viewed as the affected member before he or she was affected (3, 4, 7). Our data were accordingly analyzed in two ways.

First, the intrapair difference in total finger ridge count was obtained for each pair, resulting in 23 difference scores for the twins discordant for schizophrenia and seven for the comparison group. Because any discordance in total finger ridge count is important regardless of direction (plus or minus), the absolute value of the difference was used. A mean of these absolute intrapair differences was obtained for each group. Because of the small size of the comparison group, the unequal group sizes, and the lack of assumption of normality for the data being analyzed, a nonparametric statistic (the Wilcoxon two-sample rank sum test) was computed to test whether the mean differences in total ridge counts for the two groups were significantly different.

Second, we analyzed percent intrapair differences, because in pairs with genetically low total finger ridge counts, even a small absolute discrepancy translates into a relatively high percent difference. For the group of twins discordant for schizophrenia, the unaffected twin's total finger ridge count was used as the denominator, and the resulting value was expressed as a percentage (affected twin's total finger ridge count minus unaffected twin's total finger ridge count, divided by unaffected twin's total finger ridge count, multiplied by 100). For the seven pairs of normal comparison twins, there was no obvious reason to place the total finger ridge count of one of the twins in the denominator, so the smaller total count of the two was used (one twin's total finger ridge count minus the other twin's total finger ridge count, divided by the smaller of the two counts, multiplied by 100). This conservative approach maximized the size of the difference in the comparison group, and this maximization was in the direction of the null hypothesis. Absolute values were also used here. A mean of the percent intrapair differences in total finger ridge count was calculated for each group, and again the nonparametric Wilcoxon two-sample rank sum test was used so as to avoid assumptions about the normality of the distribution.

There was one outlier pair at more than three standard deviations above the mean in the group of twins discordant for schizophrenia, and the Wilcoxon two-sample rank sum statistic was computed for both analyses to test for significant differences with this pair removed. We also tested for any effect of gender by using a Wilcoxon two-sample rank sum test on absolute intrapair differences and percent intrapair differences in both the group of twins discordant for schizophrenia and the normal comparison group, with gender as the grouping factor. Since our hypothesis was clearly in one direction, we used the one-tailed probability value for all analyses, and alpha was set at $p<0.05$.

RESULTS

Table 1 displays total finger ridge counts, absolute intrapair differences, and percent intrapair differences for the twins discordant for schizophrenia, and table 2 shows the same data for the normal comparison twins. The results of the analyses for mean percent intrapair differences are shown in figure 3.

The mean absolute intrapair difference in total finger ridge count for the group of twins discordant for schizophrenia (12.2, SD=9.7) and that for the comparison group (4.4, SD=5.2) were significantly different

TABLE 1. Total Finger Ridge Count, Absolute Intrapair Difference, and Percent Intrapair Difference for 23 Monozygotic Twin Pairs Discordant for Schizophrenia

Twin Pair	Sex	Total Finger Ridge Count: Schizophrenic Twin[a]	Total Finger Ridge Count: Nonschizophrenic Twin[b]	Absolute Intrapair Difference	Percent Intrapair Difference
1	F	115	96	19	19.8
2	F	163	143	20	14.0
3	F	154	137	17	12.4
4	M	132	122	10	8.2
5	M	141	131	10	7.6
6	M	92	87	5	5.7
7	M	151	143	8	5.6
8	M	196	186	10	5.4
9	F	137	131	6	4.6
10	F	214	206	8	3.9
11	M	135	130	5	3.8
12	F	182	176	6	3.4
13	M	220	215	5	2.3
14	M	149	146	3	2.1
15	F	97	99	–2	–2.0
16	F	192	202	–10	–5.0
17	M	78	84	–6	–7.1
18	M	187	203	–16	–7.9
19	M	154	177	–23	–13.0
20	M	107	129	–22	–17.1
21	M	43	55	–12	–21.8
22	F	29	39	–10	–25.6
23	M	43	90	–47	–52.2

[a]Mean=135.4, SD=53.6.
[b]Mean=136.0, SD=48.9.

(z=–2.4, p=0.008). This finding was in the hypothesized direction, i.e., a greater difference in the discordant group than in the comparison group.

The mean percent intrapair difference in total finger ridge count for the group of twins discordant for schizophrenia (10.9, SD=11.2) and that for the comparison group (2.8, SD=2.9) were also significantly different (z=–2.5, p=0.006). This finding was also in the hypothesized direction.

No significant effect of gender was found in either of the two groups. The mean percent intrapair difference in total finger ridge count of the twins discordant for schizophrenia was 10.08 for the female pairs and 11.14 for the male pairs.

Also, when we recomputed the analyses of mean absolute intrapair differences and mean percent intrapair differences in ridge count between the two groups, with the outlier pair removed from the group discordant for schizophrenia (N=22), the differences between groups remained significant.

DISCUSSION

To our knowledge, this is the first report of a study in monozygotic twins of a quantitative prenatal insult marker in an adult medical condition. The monozygotic twins discordant for schizophrenia had a higher intrapair discrepancy in fingertip ridge count than the normal twin pairs; i.e., their fingerprints were significantly less "twin-like." This finding extends our previous quantitative clinical study in which we found more minor physical anomalies in the hands of the probands in the same monozygotic twin sample (36).

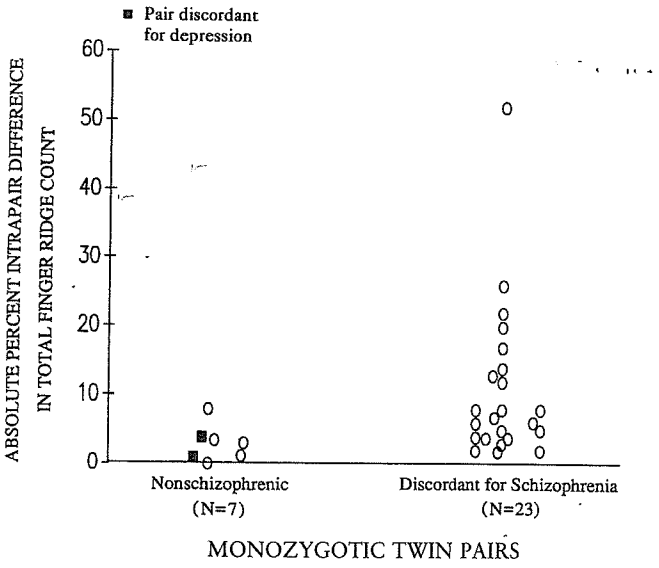
Ridge count, like height, is under polygenic control (17). Ridge count is increased, for example, in patients with monosomy of the X chromosome (Turner's syndrome), and it is decreased in Klinefelter's syndrome (47,XXY). It is also decreased with the deletion of the short arm of chromosome 5. The effect of these genetic aberrations on ridge count is presently thought to be indirect and mediated through their effect on fetal size in relation to gestational age (30). A postfertilization somatic mutation affecting second-trimester ectodermal cell migration in the affected twin or a split at the blastocyst stage as suggested by Roberts (37) are two conceivable, though unlikely, explanations for the ana-

TABLE 2. Total Finger Ridge Count, Absolute Intrapair Difference, and Percent Intrapair Difference for Seven Monozygotic Normal Twin Pairs

Twin Pair	Sex	Total Finger Ridge Count[a]: Twin 1	Total Finger Ridge Count[a]: Twin 2	Absolute Intrapair Difference	Percent Intrapair Difference
1	F	125	125	0	0.0
2	M	123	124	1	0.8
3	M	194	196	2	1.0
4	F	113	116	3	2.7
5	F	149	154	5	3.4
6	M	152	158	6	4.0
7	F	179	193	14	7.8

[a]Mean=150.0, SD=30.4.

FIGURE 3. Percent Intrapair Difference in Total Finger Ridge Count for Monozygotic Normal Twin Pairs and Twin Pairs Discordant for Schizophrenia[a]



[a]p=0.006, Wilcoxon's two-sample rank sum test.

tomical differences in ridge count and brain structure between monozygotic twins discordant for schizophrenia. Since discordance for schizophrenia in monozygotic twins is about 50%, such an explanation would assume an implausible postfertilization mutation rate of 50%. The results of the present study are more consistent with a diathesis-stressor, two-strike etiology of schizophrenia (2, 3, 10, 38–40), with differences in ridge count being a marker of the intrauterine insults that have provided the second strike. A similar two-hit etiology for some cancers has been proposed by Knudson (40).

This study suggests that the monozygotic twins discordant for schizophrenia were significantly more discordant in size than the healthy monozygotic twins during the second trimester in utero. Second-trimester conditions that could result in a brain injury coupled with a prenatal size discrepancy (and thus a ridge count discrepancy) between monozygotic twins include the following: anemia, anoxia, ischemia, maternal alcohol or drug abuse, maternal toxin exposure, and twin transfusion syndrome. All of these can produce smaller fetal size and therefore a lower total finger ridge count. In contrast, prenatal infections produce generalized fetal edema (including fingertip edema) and thus a higher total finger ridge count (24, 26). Any of these postfertilization prenatal insults, regardless of the direction in which they affect total finger ridge count, could increase the expression of genetic vulnerability to a psychotic disorder by interfering with cell migration from the germinal matrix to the cortex (41).

The literature clearly indicates that the etiology of schizophrenia in twins is not different from the etiology of schizophrenia in singletons (3). Therefore, the findings of this study should be generalizable to all patients with schizophrenia. Obviously, only a monozygotic-twin research strategy can properly control for genotype and therefore allow us to measure differences in this marker of second-trimester environmental interference with intrauterine dermal cell migration. It has been recently suggested, on the basis of epidemiological data, that some patients with the schizophrenic syndrome have been exposed to infection during the second trimester (42). However, there is a growing consensus that neither genetics nor perinatal complications alone are the sole cause of schizophrenia, even in subgroups of schizophrenic persons (38). The results of this study are consistent with the multifactorial diathesis-stressor, two-strike model of the etiology of schizophrenia (2, 3, 10, 38, 39, 41).

We demonstrated fingertip ridge count evidence for second-trimester insult in about one-third of the monozygotic twin pairs who were discordant for schizophrenia. Not all of the discordant twin pairs displayed this anatomical marker of second-trimester insult. This heterogeneity in schizophrenia is not surprising, because the expression of a psychosis-related gene or genes can probably be increased also by postnatal insults or by prenatal insults that would not alter fetal size (and thus ridge count). Nevertheless, ridge count may be a more sensitive and more specific marker of second-trimester size in monozygotic twins than either minor physical anomalies or even birth weight. A twin whose size was retarded during the second trimester can easily "catch up" to the unaffected twin in birth weight during the third trimester, because 75% of birth weight is gained in the third trimester (18, 31, 43). This twin study provides direct anatomical evidence that phenotypic schizophrenia in genetically exposed individuals may be associated with various (probably heterogeneous) insults that also affect size in relation to gestational age during the second prenatal trimester.

Ridge count may serve as a moderately sensitive but most specific marker of second-trimester fetal size in future studies of monozygotic twins. Fingertip ridge counts should be obtained and analyzed as a dependent variable in all future studies of psychiatric disorders in monozygotic twins. If replicated, this twin study may also have public health implications regarding the importance of second-trimester prenatal care in preventing the expression of severe adult, adolescent, and child behavioral disorders.

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