obstetric complications and twin studies of schizophrenia: clarifications and affirmations

Torrey (1977) believes that we (Gottesman and Shields 1976a and 1976b) made erroneous statements about birth weight differences as a cause of discordance in identical (M2) twin pairs where one was schizophrenic, and about the unlikelihood that perinatal insults are specific etiological factors in schizophrenia. His erroneous conclusions seem to stem from his misinterpretation of the twin literature on birth weight differences and from his loose use of the term "specific etiology."

Two sets of findings are frequently cited by those who favor the hypothesis claiming the special importance of obstetric complications (OCs) in schizophrenia: the marked tendency in the NIMH discordant MZ twin studies of Pollin and colleagues for the affected twin to have had the lighter birth weight, and the speculation by Mednick and colleagues that OCs in their high risk study are among the most critical environmental factors that interact with a genetic predisposition. As we saw it, in our Schizophrenia Bulletin review (1976a), these reports were not confirmed, and are therefore misleading. Our efforts here to clarify and to affirm our analyses must be brief. Important critical papers have appeared recently on obstetric factors in schizophrenia by McNeil and Kajj (1976) and on the meaning of specific etiology for behavior genetic and medical syndromes by Meehl (1977); the reader is urged to consult both papers.

There are many ways of playing around with twin data, but it is obscure how Torrey calculated that we had 15 discordant pairs with information on birth weights in our study (Gottesman and Shields 1972). We had 11 discordant MZ pairs altogether (final consensus diagnoses of schizophrenia) with birth weight information for seven, including two where the twins were reported to have had equal weights. We omitted the latter two pairs even though they weaken our effort to contradict the hypothesis that the schizophrenic member of discordant pairs is the lighter at birth. Of the five remaining discordant pairs, the affected twin was the lighter in four (MZ 4, 11, 14, and 18), the heavier in one (MZ 5). Results are in the hypothesized direction, even more so than in Torrey's analysis. To these five pairs we added the four concordant MZ pairs in which there was a marked, objective difference in severity of illness. We did so on logical grounds. If biological factors such as relatively low birth weight can influence the occurrence of schizophrenia, we would also expect them to influence the course of the illness. In these added pairs the more severely affected twin had the lighter weight in only one pair (MZ 6) and the heavier in three (MZ 2, 13, 23), including the pair least concordant (MZ 23) and the pair with the largest weight difference of all (MZ 2, 7 lbs and 3½ lbs). Incidentally, we found no tendency for the DZ schizophrenics in our sample to have lower birth weights than their nonschizophrenic co-twins.

Among the five pairs from Slater's (1953) study counted by Torrey as discordant, the last three (167, 169, 271) are dizygotic and do not belong in an analysis that examines putative contributory causes when genotype is held constant.

Kringlen (1967, p. 119) reported nine discordant MZ pairs in which the schizophrenic was lighter at birth and 12 discordant MZ pairs in which the affected was heavier. Torrey deletes some pairs on diagnostic grounds, and then claims to have found 11 pairs with the schizophrenic lighter at birth.¹ Kringlen's

¹This may not be as impossible as it seems, however, since the information in the privately published case histories does not appear to tally with Kringlen's tabulation. It does not tally with Torrey's analysis either.
own conclusion was that his and other studies showed no marked correlation between such factors as birth weight and difficult birth and the later development of schizophrenia. In fact, in a subset of his MZ pairs discordant for paranoid schizophrenia, the affected twin had been the heavier at birth in the ratio 8:1.

Torrey combined the highly selected, unrepresentative NIMH sample plus some single case reports from the literature with the systematically ascertained series of twins, based on defined populations of schizophrenics, used by us in our table 5 (Gottesman and Shields 1976a). The mode of ascertainment of the former virtually guarantees noncomparability with the latter. The criticisms so far of Torrey's analysis of the birth weight problem suggest that he has added apples, oranges, and potatoes (DZ pairs); we believe that little weight (light weight?) should be given to his table 1 so far as the systematically ascertained twin samples are concerned.

For the record, we show in table 1 how we reached the total of 43/87 (49 percent) reported in our review (1976a, p. 379). The data of other studies were taken as reported by the investigators themselves. They all included the comparison of discordant pairs differing in severity except Tienari, none of whose 16 pairs were regarded as discordant for schizophrenia in 1963, and Kringlen. Following Torrey's suggestion, we have now attempted to see what the figures would look like for the systematic studies if we restricted ourselves to discordant twin pairs, omitting discordant pairs differing in severity and including information on followup (Tienari 1971). Our best estimate yields a proportion of 26/48 or 54 percent of the discordant pairs where the schizophrenic was the lighter at birth. Inouye's (1963) sample dis-

Table 1. Association of birth weight differences and schizophrenia in the systematically ascertained twin studies (as analyzed by Gottesman and Shields 1976a)

<table>
<thead>
<tr>
<th>Twin study</th>
<th>Schizophrenic (or more severe) twin lighter at birth</th>
<th>Schizophrenic (or more severe) twin heavier at birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slater (1953)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Inouye (1963)</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Tienari (1963)</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Kringlen (1967)</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Gottesman and Shields (1972)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Fischer (1973)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total systematic studies</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>

appears from such an analysis since the necessary data on completely discordant pairs cannot be abstracted. (We will provide case numbers for our best estimate to devotees of the problem on request.)

In regard to the question about perinatal insults we may actually agree with Torrey's conclusions but not with his formulation of the problems. According to McNeil and Kaij (1975) the kinds of perinatal risk characteristics obtained from such retrospective studies as Pollin and Stabenau's (1968) pale in the face of prospectively designed studies in obstetric psychiatry. (In the former's own retrospective study 57 separate OCs are examined.) Few subjects, they say, either at high or low risk, go through the reproductive sequence without showing something that might have seemed highly instructive had it been found retrospectively in a schizophrenic. We are reminded here of the sweeping claims formerly made by Rankian enthusiasts about the role of the birth trauma in personality formation. There are, however, suggestions from twin studies that major perinatal insults may sometimes be associated with schizophrenia or with augmenting its severity. The proband of our fraternal pair DZ 26 (Gottesman and Shields 1972) weighed only 3½ lbs at birth, her sister 6-3/4 lbs; delivery was breech, and she had a bilateral ptosis and "twisted right leg." She was rejected by her parents, while her twin differed on each count—attractive, successful, well married, and, at followup, self-confident. The proband's consensus diagnosis was clear schizophrenia, although one of the chart diagnoses was paranoid state due to a birth injury. In our afterthoughts about the case we said:

2 Taking account of followup information (Belmaker et al. 1974), the corresponding proportion in the NIMH sample is considerably higher: 10/12 or 83 percent. However, even when we add the six discordant pairs from the literature included in Torrey's table, in five of which the schizophrenic was the lighter at birth, the association with lower birth weight was not significantly more marked than in the systematic series analyzed above.

She was in all senses the ugly duckling. Perhaps nothing could prevent the vicious circles in her life which finally led her to schizophrenia; without a genetic predisposition for schizophrenia we would have predicted some other kind of psychiatric disability. [p. 192]

Twins are more liable to OCs than
singleton, with MZ twin pregnancies and deliveries more at risk than DZ. Moreover, males are at greater risk than females. If OCs had a specific etiological role in schizophrenia and were not just a moderator variable or contributor to a concatenation of causes added to the genetic predisposition, we would have expected higher prevalences of schizophrenia in MZ males than MZ females, in MZs than DZs, in males than females, etc. Though such predictions have been confirmed for mental retardation, they have not been supported for schizophrenia.

Until recently there was no reliable retrospective or prospective information on the number of OCs in schizophrenics themselves. Information on the offspring of schizophrenic patients (high risk children) has many limitations and findings are inconsistent. When complications or neonatal deaths are found in excess in a particular sample, they could implicate the genotype of the child, intrauterine environmental factors, medication toxicity (Rieder et al. 1975), or unreported attempts at self-abortion. The crux of the matter is that until high risk infants are followed up well into adulthood, we shall not know whether those who had the OCs, even when combined with childhood behavior problems or deviant psychophysiology, will be the ones who become affected with schizophrenia (Shields 1977). The combination of reasonable indicators in a unique configuration within a high risk group can be suggestive only (Hanson, Gottesman, and Heston 1976).

We agree with most of what Torrey says in the first paragraph of section 2; much of it seems to derive from Hanson, Gottesman, and Heston (1976). But what about the children of schizophrenic fathers? They are no less at risk for schizophrenia than the offspring of schizophrenic mothers. In the Kety et al. (1975) research the paternal half-sibs do not differ in overall rates of psychopathology from the maternal half-sibs of their schizophrenic index cases. Torrey has been misled into construing “at risk” to refer to the children of schizophrenic mothers only: Mednick et al. (1973), Mirdal et al. (1974), Hanson, Gottesman, and Heston (1976) and, recently, Mirdal et al. (1977) using the Rosenthal et al. (1968) adoptee sample also studied the children born to non-schizophrenic mothers impregnated by men who were the schizophrenic index cases.

OCs and other biological factors such as viral infections are difficult enough to establish as causes of childhood psychiatric disorders other than epilepsy and mental retardation (see Rutter and Hersov 1977), let alone in the case of a condition that may have its onset some 30 or 40 years later. If one accepts the utility of the concept of a continuum of re-productive casualty (Pasamanick and Knobloch 1960), schizophrenia must surely be at its extreme and least specific end. We concur with McNeil and Kají's (1976) reservations and conclusion that OCs are independent stressful factors that seem to interact with the genetic influences and are a risk-increasing factor to be taken seriously in the etiology of schizophrenia. But, we add, which ones, how seriously, and in what proportion of cases?

A useful mental exercise for both commentators and researchers on the etiology of schizophrenia is to ask themselves the following questions about putative etiological factors: What percentages of false positives and false negatives do the factors generate? Is the factor one-way quasi-pathognomonic, i.e., does its presence indicate (rule in) schizophrenia? Is it two-way pathognomonic, i.e., does its absence also indicate that schizophrenia can be excluded? The answers will suggest where on a continuum of specific etiology to strong influence to moderator variables (Meehl 1977) the putative etiological factor belongs.

Torrey's comments about viral hypotheses and the importance of the HL-A complex for generating further hypotheses are well intended. We would be more sanguine in our views if such suggestions were at the same time put forth by practicing virologists and immunogeneticists together with analogs from somatic illness that are credible. Torrey and Peterson (1976) in the Schizophrenia Bulletin admit there is so far “not even enough evidence to indict viruses.” More work will be and should be done on the role, if any, of the hundreds or thousands of genes linked to the HL-A complex; the system is a happy hunting ground for geneticists, given its luxuriant polymorphisms. Its potential for providing endophenotypes of interest for all kinds of genetically conditioned disorders cannot be discounted. So far the results for schizophrenia are highly inconsistent and badly in need of controlled replications with larger samples, let alone some guiding theory.

We thank Dr. Torrey for giving us a challenge to clarify a small part of our review. We welcome Professor Ødegaard's (1977) informed and balanced comments: they are ideal for restoring order to the scene.

References


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