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## Family History and Birthweight in Monozygotic Twins Concordant and Discordant for Psychosis

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**Abstract.** In a sample of monozygotic twins, intrapair differences in reported birthweight were larger in those pairs discordant for later psychosis, compared to pairs concordant for psychosis. A trend towards less family history of psychiatric disorder was also found in the discordant pairs.

**Key words:** Psychosis, Birthweight, MZ Twins

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### INTRODUCTION

One favoured etiological model for the functional psychoses is a multifactorial model [16] in which the illness phenotype appears when individual "liability" exceeds a certain threshold. This liability is a hypothetical quantity whose distribution within the general population is assumed to be normal, and which is a sum of environmental and genetic, presumably polygenic, factors. Multiple-threshold versions of this model are testable and have been used to explain familial distribution of both affective disorders [3] and schizophrenia [10]. Within the multifactorial model, it is to be expected that affected individuals will vary in the degree to which environmental and genetic factors, respectively, contribute to liability. Although this variation might be predicted by the model, its consequences have been little explored and possible environmental causes have received scant attention.

The study of monozygotic (MZ) twins discordant for psychosis offers a potentially powerful strategy for the identification of environmental agents [2]. The very existence of such twins demonstrates indisputably that environmental factors are important, but few studies have made adequate attempts at identifying these [7]. One obvious limitation is the rarity of suitable sub-

jects. Nonetheless, a small amount of data has slowly emerged which allows some speculations about the relationship between genetic and environmental influences. Rosenthal's reanalysis [19] of Slater's series of MZ twin pairs with a schizophrenic proband [20] suggested that similar illness in family members other than the cotwin was significantly less common if the twins were discordant, rather than concordant. This caused Rosenthal to propose that these represented two types of schizophrenia, one predominantly "genetic", the other not. Other studies have attempted to examine possible environmental agents peculiar to the proband, within discordant pairs. Whilst some authors have emphasised psychosocial factors as likely environmental determinants [6], others believe that organic processes of environmental origin will prove more important in explaining the development of psychosis in one twin but not the other. Recent work using computed tomography in MZ twins concordant and discordant for schizophrenia, as well as normal MZ twins and DZ twins [14] supports the latter view by demonstrating that, although cerebral ventricular size usually shows high intrapair correlation in MZ twins, this correlation is diminished in pairs discordant for schizophrenia such that the affected twin shows relative ventricular enlargement. Further research has implied that this ventricular enlargement is inversely related to the presence of a family history of psychosis in both twin [15] and singleton [9] samples, and directly related to early histories of neurological insult, particularly at or around the time of birth [13].

Within the paradigm of discordant MZ twins, intrapair differences in birthweight and obstetric complications have been sought and, some would claim [11,25], found. Over fifty years ago Rosanoff and colleagues [18] pointed to the etiological importance of adverse obstetric events in twin pairs later discordant for schizophrenia, and cited post mortem atrophic brain changes found in some cases of schizophrenia as evidence in support of their proposal. Since then, the question of whether obstetric, especially birthweight, differences in the histories of twins might be an important environmental factor in accounting for subsequent discordance for psychosis has been hotly debated, not least because of the paucity of actual data. A compilation of the birthweight data from four series of discordant MZ twins is presented in the Table, in the manner usually used, of qualitative intrapair comparison (which twin was lighter?). In this compilation the strategy of including concordant pairs discordant for severity which has been invoked previously [6] has been avoided. A trend towards the affected twin having been lighter at birth can be seen, but this is not as striking as previous commentators have claimed. However, such qualitative comparisons fail to make use of all available data: qualitative analyses might prove more informative.

The current study set out to examine these factors in a preliminary sample of psychotic MZ twins drawn from a new series, with the general hypothesis that manifest genetic factors would be more evident in concordant pairs whereas differential early environmental factors would be discerned better in discordant pairs.

## METHOD

Cases were drawn from the Maudsley Hospital twin register, which has in the past furnished the material for two well known series of psychotic twins prior to 1967, those of Slater [20] and Gottesman and Shields [4]. All patients who attend the Bethlem Royal and Maudsley Hospitals are asked routinely at initial presentation whether or not they are of twin birth and, if so, whether their cotwin is alive and of which sex. The coded data forms the basis of a consecutive series of twin probands. Probands who have been ascertained since 1967 and who have suffered a functional psychosis are presently being followed up, with their cotwins, in

a prospective interview study. The interview includes the administration of a diagnostic instrument (the Schedule for Affective Disorders and Schizophrenia, lifetime version [22]), the collection of a semistandardised family pedigree and obstetric and early developmental data from the mother where available. Zygosity is established by serological matching of six blood antigens or response to a physical resemblance questionnaire including items shown to be highly predictive of zygosity [24].

A sample of twin pairs in whom hand preference had been established was isolated for the purpose of a study investigating a reported association between discordance for right-handedness and discordance for diagnosis. The same sample was used for this study. Selection criteria were therefore: 1) a documented episode of illness in the proband, characterised by delusions, hallucinations or formal thought disorder without acquired cognitive impairment ("functional psychosis"), 2) available hand preference data, and 3) a living cotwin at the time of ascertainment. A total of 65 pairs fulfilled these criteria, of whom 31 were MZ.

Our first prediction was that a family history of major psychiatric disorder would be more prevalent in those MZ pairs concordant for psychosis. In order to test this, the rate of reported psychiatric inpatient admission of one or more first- or second-degree relatives (excluding the cotwin) was compared in the concordant and discordant groups. The second prediction was that early environmental factors operating differentially within pairs would be more evident in the histories of those pairs discordant for psychosis. This was tested using birthweight data as an indicator of differential early environmental hazard. These data, along with other obstetric information, were collected routinely from the mother at interview or by questionnaire. Birthweight was recorded in British imperial units of pounds and ounces, converted to grams for the purposes of this study. These data were analysed both casewise and pairwise, in categorical intrapair comparisons (which twin was heavier?) and examination of quantitative intrapair weight differences (by how much was one twin heavier?) in the concordant and discordant groups.

## RESULTS

Of the 31 MZ twin pairs in the sample, 13 (42%) were concordant and 18 discordant for functional psychosis. These figures are in broad agreement with previous studies, although it must be remembered that this sample was not, in itself, a consecutive series.

### Family History Data

Reliable data concerning family history of psychiatric admission were not available for one discordant pair. Psychiatric admission in a first- or second-degree relative was reported in 9 of the 13 concordant pairs (69%) compared with 8 of the 17 discordant pairs (47%). This trend was in the predicted direction, although not as compelling as that reported by Rosenthal [19].

### Birthweight Data

Data from maternal reports of birthweight were unavailable in 5 concordant and 5 discordant pairs. Examination of the data available for the 13 discordant pairs showed, firstly, that the affected twin was lighter at birth in 7 pairs, heavier in 3, and of equal weight to the cotwin in 3 pairs. Again, this trend was in the predicted direction and was similar to that reported

**Table. Review of studies giving relative birthweights in discordant psychotic MZ twins**

	Ill twin lighter	Ill twin heavier	Equal weights
Tienari (1963)	8	6	0
Kringlen (1967)	9	12	4
Mosher et al (1971)	12	3	0
Gottesman & Shields (1972)	5	0	2
<b>TOTAL</b>	<b>34</b>	<b>21</b>	<b>6</b>

in other studies (Table).

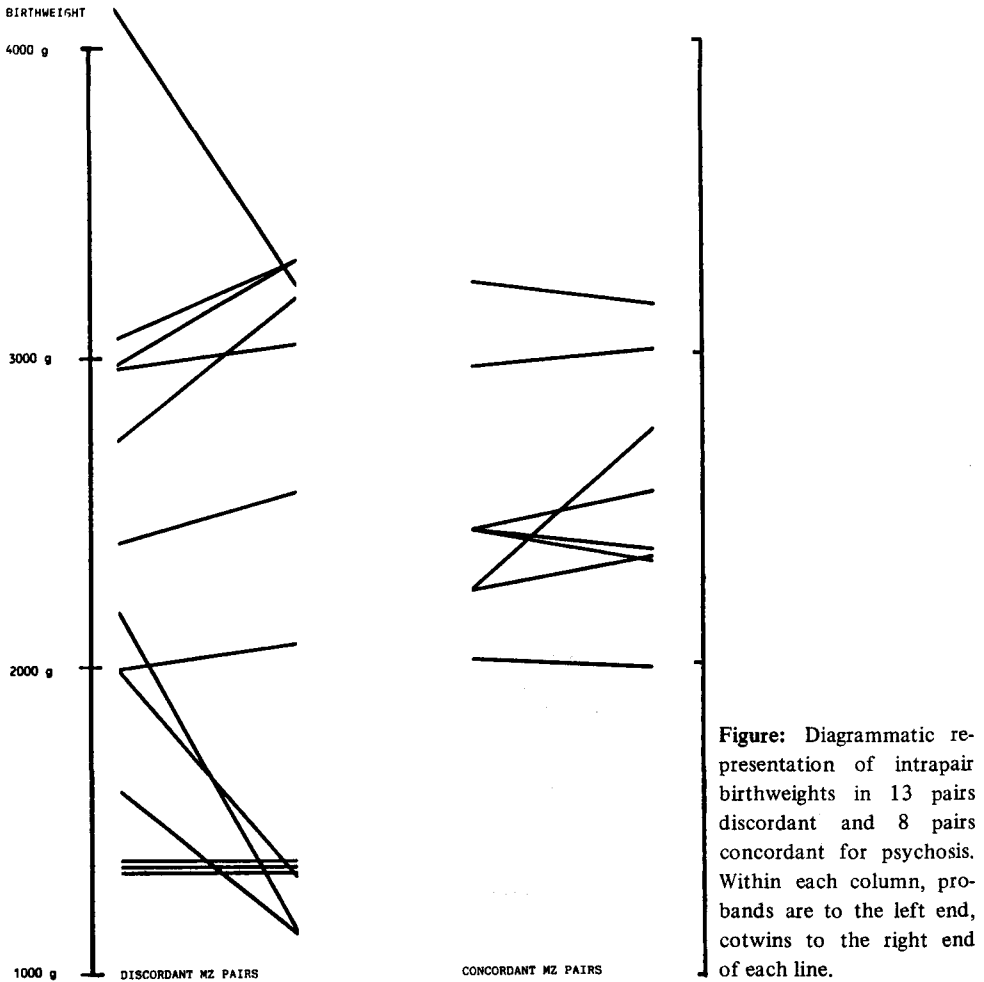
Secondly, casewise analysis of the actual birthweights revealed little difference between members of concordant pairs ( $n = 16$ , mean 2530 g, SD 383 g), affected members of discordant pairs ( $n = 13$ , mean 2294 g, SD 828 g) and unaffected (nonpsychotic) members of discordant pairs ( $n = 13$ , mean 2166 g, SD 916 g).

The third and most informative analysis was a comparison between the intrapair birthweight differences in the discordant and concordant pairs respectively. These data are presented in the Figure. The mean reported birthweight difference in the discordant pairs was 312 g (SD 331 g), more than four times that in the concordant pairs (mean 78 g, SD 33 g). This difference approached significance (2-tailed  $t$  test of means = 1.90,  $P = 0.07$ ). Equal weights were reported in three of the discordant but none of the concordant pairs.

## DISCUSSION

These preliminary results from a selected sample of MZ twin pairs in whom the proband suffered from a functional psychosis lend qualified support to the hypothesis that liability for the disorder is higher in concordant pairs, while a differential environmental contribution is of greater importance in discordant pairs. A manifest family history of severe psychiatric disorder indicated by reported inpatient admission was taken to be an empirical marker of genetic predisposition. Birthweight discrepancy was chosen as a marker for differential environmental effects. It should be noted that both of these measures can be criticised on theoretical and practical grounds, and the results are open to different interpretations. The family history method of collecting data is imperfect, although probably adequate [1], and, clearly, such data will be influenced by the number and age of the relatives themselves. It may be, for instance, that some pairs are discordant as a consequence of too short a period of follow up: such pairs are likely to be younger than concordant pairs and so have younger relatives also. Such an artefact could contribute to the lower family history reported in discordant pairs.

Even more than family history data, maternal reports of birthweight twenty or more years after the event are of suspect reliability. Such evidence as does exist, however, suggests that birthweight is more accurately recalled than most obstetric variables [17]. Certainly, the examination of absolute intrapair differences precludes an important criticism of the previous



**Figure:** Diagrammatic representation of intrapair birthweights in 13 pairs discordant and 8 pairs concordant for psychosis. Within each column, probands are to the left end, cotwins to the right end of each line.

practice of simply noting categorical differences in birthweight, namely that, in hindsight, the mother of a discordant pair may erroneously attribute the lighter weight to the affected twin in an “effort after meaning”. The possibility that a similar systematic error in recalling concordant weights in concordant pairs might be at work is unlikely, since in none of the concordant pairs in this sample were equal weights reported. Even setting aside its theoretical limitations, the presence of a positive family history can tell us nothing about the precise mechanisms by which genes contribute to psychosis. In the same way, the observation of a greater mean variation in birthweight between members of discordant pairs can tell us little about the actual environmental factors operating. One possibility is that the intrauterine processes which cause unexpected birthweight discrepancies between members of an MZ twin pair may also bring about developmental anomalies within the nervous system of one twin which increase the risk of later psychosis. Another possibility is that one effect of discrepant birthweight is to increase the likelihood of complications at birth, such as preterm labour, abnormal presentations and delayed deliveries, which lead to cerebrovascular sequelae in one twin which again

predispose to later illness. Increased rates of obstetric complications in the histories of the affected twin in pairs discordant for psychosis have been claimed [11] and there is increasing evidence that the effect of such complications are significant in some psychoses and in causing the radiological brain abnormalities which often accompany them [13].

These data are still open to other interpretations which invoke psychosocial rather than organic mechanisms; it has been shown, for example, that birthweight of infant twins is important in determining maternal attitude and the greater the discrepancy in birthweight the more the mothers behaviour towards each twin differs [21].

In conclusion, these preliminary findings suggest that an unexpectedly large discrepancy in birthweight characterises MZ twins later to be discordant for psychosis. The mechanism by which this effect is exerted is obscure but likely to involve environmental agencies acting differentially within twin pairs. The family history data give qualified support to the notion that genetic factors are of relatively greater importance in concordant pairs.

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## REFERENCES

1. Andreasen NC, Rice J, Endicott J, Reich T, Coryell W (1986): The family history approach to diagnosis. *Arch Gen Psychiatry* 43:421-429.
2. Eaves LJ, Kendler KS, Schulz SC (1986): The familial sporadic classification: Its power for the resolution of genetic and environmental aetiologic factors. *J Psychiatr Res* 20:115-130.
3. Gershon ES, Hamovit JJ, Guraff JJ et al (1982): A Family study of schizoaffective, bipolar 1, bipolar 2, unipolar and normal control probands. *Arch Gen Psychiatry* 39:1157-1167.
4. Gottesman II, Shields J (1972): *Schizophrenia and Genetics: A Twin Study Vantage Point*. New York: Academic Press.
5. Gottesman II, Shields J (1977): Obstetric complications and twin studies of schizophrenia: Clarifications and affirmations. *Schizophrenia Bull* 3:351-354.
6. Gottesman II, Shields J (1982): *Schizophrenia: The Epigenetic Puzzle*. Cambridge: Cambridge University Press.
7. Kringlen E (1967): *Heredity and Environment in the Functional Psychoses*. London: William Heinemann.
8. Kringlen E (1986): Status of twin research in functional psychoses. *Psychopathol* 19:85-92.
9. Lewis SW, Reveley AM, Reveley MA, Chitkara B, Murray RM (1987) The familial sporadic distinction as a strategy in schizophrenia research. *Br J Psychiatry*, in press.
10. McGue M, Gottesman II, Rao DC (1983): The transmission of schizophrenia under a multifactorial threshold model. *Am J Hum Genet* 35:1161-1178.
11. McNeil TF, Kaij L (1978): Obstetric factors in the development of schizophrenia: complications in the births of preschizophrenics and in reproduction by schizophrenic parents. In Wynne LC, Cromwell RL, Matthysse S (eds): *The Nature of Schizophrenia*. New York: Wiley.
12. Mosher LR, Pollin W, Stabenau JR (1971): Identical twins discordant for schizophrenia. *Arch Gen Psychiatry* 24:422-430.
13. Murray RM, Lewis SW, Reveley AM (1985): Towards an aetiological classification of schizophrenia. *Lancet* i:1023-6.
14. Reveley AM, Reveley MA, Clifford CA, Murray RM (1982): Cerebral ventricular size in twins discordant for schizophrenia. *Lancet* i:50-541.
15. Reveley AM, Reveley MA, Murray RM (1984): Cerebral ventricular enlargement in non-genetic schizophrenia: A controlled twin study. *Br Psychiatry* 144:89-93.
16. Reich T, Cloninger CR, Guze SB (1975): The multifactorial model of disease transmission: description of the model and its use in psychiatry. *Br J Psychiatry* 127:1-10.
17. Robbins LC (1963): The accuracy of parental recall of aspects of childdevelopment and of child rearing practices. *J Abnorm Soc Psychol* 66:262-270.
18. Rosanoff AJ, Handy LM, Plesset I, Brush S (1934): The etiology of so-called schizophrenic psychoses with special reference to their occurrence intwins. *Am J Psychiatry* 91:247-286.

19. Rosenthal D (1959): Some factors associated with concordance and discordance with respect to schizophrenia in monozygotic twins. *J Nerv Ment Dis* 129:1-10.
20. Slater E (1953): Psychotic and Neurotic Illnesses in Twins. Medical Research Council Special Report, Series No. 278. London: Her Majesty's Stationery Office.
21. Spillman JR, (1987): Birthweight effects on twin temperament and maternal rewards. *Acta Genet Med Gemellol*, in press.
22. Spitzer R, Endicott J, Robins E (1975): Research Diagnostic Criteria, Instrument No. 58. New York: NY State Psychiatric Institute.
23. Tienari P (1963): Psychiatric illnesses in identical twins. *Acta Psychiatr Scand Suppl* 171:9-195.
24. Torgersen S (1979): The determination of twin zygosity by means of a mailed questionnaire. *Acta Genet Med Gemellol* 28:225-236.
25. Torrey EF (1977): Birth weights perinatal insults and HLA types: return to "original sin". *Schizophr Bull* 3:347-351.

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