Confirming Unexpressed Genotypes for Schizophrenia

Risks in the Offspring of Fischer's Danish Identical and Fraternal Discordant Twins

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• **Margit Fischer reported in 1971 that the risk of schizophrenia in the offspring of her Danish schizophrenic monozygotic twins and their normal cotwins was equal and not different from the risks in the children of schizophrenics in the literature. All of her identical and fraternal twins who had children and all of their offspring have been followed up through the Danish National Psychiatric Register as of 1985, some 18 years after study by Fischer. The morbid risk (age-corrected) for schizophrenia and schizophrenia-related disorders in the offspring of schizophrenic identical twins is 16.8%; it is 17.4% in their normal cotwins' offspring. The risks in the offspring of schizophrenic fraternal twins and their normal cotwins are 17.4% and 2.1%, respectively. The results suggest that discordance in identical twins may primarily be explained by the capacity of a schizophrenic genotype or diathesis to be unexpressed unless it is released by some kinds of environmental, including nonfamilial, stressors. Sporadic cases and phenocopies caused by cerebral abnormalities, diseases, or viruses would thus be deemphasized as necessary or sufficient explanatory causes for schizophrenia in our study but could account for some of the remaining discordance. Infrequent phenocopies should encourage linkage researchers, but unexpression of genotypes will frustrate them.**

(*Arch Gen Psychiatry.* **1989;46:867-872**)

The etiology of schizophrenia is not yet known, but many converging lines of evidence from family, twin, and adoption studies implicate genetic factors as the most important of the multifactorial causes in a diathesis-stressor model.[1-4] Without definitive knowledge about etiology, genetic counseling as well as genetic model fitting[5,6] are dependent on empirical risks observed in the numerous family and twin studies conducted since reasonably scientific methods were first used in 1916.[7]

Family studies pooled from more than 20 Western European studies over the past 62 years[8] have shown lifetime morbid risks (age-corrected) of about 13% in the children of schizophrenics, 9% in siblings, and 6% in parents compared with a general population risk of close to 1% for a conservative but not restrictive definition of schizophrenia.[9,10] Four recent studies of first-degree relatives have challenged the received wisdom about the familiality of schizophrenia (3 in the United States, 1 in Greece) but cannot be given serious credence (see Kendler[11] for a critical review): the statistical power was often low due to the small number of "lifetimes at risk" observed among both relatives and controls; controls evaluated by the same standards as probands' relatives were not always available; the information available for probands' relatives may have been based on telephone interviews or "second hand" from patients' records; and a focused search for schizophrenia disorders was not generally a part of the protocols.

All of the morbid risk values could only be calculated from the carriers of the genotype for schizophrenia who expressed that genotype to a degree that the relevant phenotype could be recognized. Incomplete expression or penetrance leads to methodologic difficulties for genetic modelers and for formal gene linkage strategies because they will result in an unknown number of misclassified genotypes (false-negatives or "pseudonormals") in the pedigrees of schizophrenics and of controls. The study of the adult offspring born to concordant and discordant monozygotic (MZ) or identical and dizygotic (DZ) or

Accepted for publication December 8, 1988.

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Presented in part before the Fifth International Congress on Twin Studies, Amsterdam, the Netherlands, September 19, 1986; the Seventh International Congress of Human Genetics, Berlin, West Germany, September 26, 1986; and the American Society of Human Genetics, San Diego, Calif, October 9, 1987.

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same-sex fraternal twins from pairs affected with schizophrenia produces unique evidence for exploring the hypothesis that the genotype for schizophrenia can remain unexpressed in the clinical phenotype throughout the life span. The strategy of studying the offspring of twins discordant for schizophrenia combines elements of the classic twin, family, and adoption strategies. The offspring of partners of a pair of identical twins are related to both twin partners as first-degree relatives who share half of their genes; the offspring of partners of a pair of fraternal twins are related to the fraternal cotwins as second-degree relatives who share one fourth of their genes. For both twin types the offspring of the normal cotwins share little to none of the within-family exposure to a schizophrenic parent.

If the observed risk to the offspring of schizophrenic identical twins were like that shown for offspring of probands generally and if the risk to the offspring of their genetically identical but clinically normal nonschizophrenic cotwins were close to the population base rate of 1%, it would indicate that nongenetic within-family factors have the power to produce schizophrenia, and/or it would raise the question of etiologic heterogeneity to allow for nongenetic phenocopies. If, on the other hand, the risks to the two classes of MZ offspring were both high and equal to each other, it would undermine any significant etiologic role for the unshared factor of a schizophrenic parent; it also would demonstrate that schizophrenia-prone genotypes can be completely unexpressed in parents but can be transmitted and expressed in their offspring who encounter putative triggers or releasers for their liabilities. The corresponding risks for the offspring of same-sex fraternal twins concordant and discordant for schizophrenia will serve as control values for first- and second-degree relatives of schizophrenics when the sources of information about psychiatric status are the same as those used to evaluate the offspring of the identical twins. A major goal of this strategy is to try to differentiate between genetic factors that are posited to be necessary but not sufficient for the development of schizophrenia and other factors that may be neither necessary nor sufficient, but that may well be risk-increasing factors, triggers, exacerbators, or contributors to severity or poor outcome in those individuals with a genetic diathesis.

SUBJECTS AND METHODS

The strategy of studying the offspring of twins was introduced to psychiatric genetics by Margit Fischer[12,13] in her Danish twin study of schizophrenia some 18 years ago. More recently it has been used by one of us (A.B.)[14] in a Danish twin study of manic-depressive disorders. After the untimely death of Fischer in 1983, a register and case record follow-up study of all her twin probands and cotwins and all of their offspring was carried out, adding 18 more years of observation time (as of February 1985) to the sample and permitting all the twins and almost all their offspring to traverse the usual risk period for the development of schizophrenia, ages 15 through 45 years. The fraternal twins' offspring were also added to the follow-up sample; their offspring were too young in 1967 to yield much information.[13(p62)] (Dizygotic twins tended to be younger than MZ twins in this sample, and schizophrenics-to-be who reproduced mainly had their children before their first hospitalization, while normal cotwins had their children over the whole reproductive period.)

Denmark is a fairly ideal country in which to conduct record research. The tradition of recording medical statistics for mental illness and mental retardation dates back to 1843 in a pilot fashion. Systematic registration began in 1938, but the system was not computerized until 1969. Currently, 86 institutions report to the National Psychiatric Register[15] on about 35 000 inpatient admissions and 5000 day-hospital patients per year; the national population is 5.5 million. In 1910 the population of Denmark was 2.76 million, with only 7 reporting hospitals. With the help of the nationwide system of local person registers, it was possible to obtain information about current addresses or dates of emigration or death for every inhabitant. The National Twin Register was begun by Harvald and Hauge[16] in 1954 and goes back, using parish-maintained birth registers, to 1870. Death certificates since 1948 (with incomplete data before that time) were obtained systematically from central registration.

Table 1.—Fischer's Danish Schizophrenic Twin Sample

Zygosity	No. of Twin Pairs M	F	Total
Monozygotic	10	11	21
Dizygotic	20	21	41
Total	**30**	**32**	**62**

Table 2.—No. of Reproducing Twins by Zygosity and Diagnosis

	No. of Twins			
	Schizophrenic*		Normal†	
	Reproducing	Total	Reproducing	Total
Monozygotic	12‡	31	7‡	11
Dizygotic	11§	49	21‡	33
Total	**23**	**80**	**28**	**44**
Reproductive rate, %	29		64	

*Includes schizophrenialike disorders (see text).
†Includes nonpsychotic disorders (see text).
‡Includes 1 emigrant to the United States with all children born abroad.
§Includes 1 man with 3 illegitimate, untraceable children.

By cross-matching the Danish Twin Register cohort born in the half century between 1870 and 1920 for pairs not broken by death by age 6 years (11 288 same-sex pairs) with the Psychiatric Register, an unselected sample of 349 twin pairs was obtained in which one or both partners had been admitted for a mental disorder. The final sample of 62 schizophrenic pairs in which one or both partners had been admitted for schizophrenia is shown in Table 1; it excludes 8 pairs with undetermined zygosity. Zygosity was determined by either blood grouping or questionnaire information, eg, about "being as like as two peas in a pod or two drops of water," and mistaken identity. The accuracy of questionnaire information is 0.95 compared with blood typing.[16]

Fischer's diagnoses of schizophrenia in the twins were accepted. Her diagnoses were made clinically according to the guidelines of the *International Classification of Diseases*, eighth edition (*ICD-8*), before the modern emphasis on operational criteria in the Research Diagnostic Criteria and *DSM-III-R*.[17,18] The index cases of schizophrenia and the fully concordant cotwins were described as process schizophrenics. Cotwins concordant by broader criteria had schizophrenia-related disorders, which for the reproductive MZ cotwins included a male with atypical psychosis, probably simple schizophrenia; a male with paranoid psychosis, probably paranoid schizophrenia; and a male with episodic schizophreniform psychosis with affective symptoms, probably schizoaffective schizophrenia. The reproductive DZ cotwins included one male with atypical psychosis, probably atypical schizophrenia. For diagnosing the offspring, all case records for all admissions, death certificate information, and family history information other than parental diagnosis were reviewed. To maintain continuity with Fischer's design, the guidelines of *ICD-8* currently in use in Danish psychiatric practice were followed for diagnosis of schizophrenia and schizophrenia-related disorders in the offspring. All such cases in the offspring were also diagnosed using the criteria in *DSM-III-R*.

All probands and their concordant cotwins are considered affected, while their nonconcordant cotwins are considered normal; this definition of "normality" includes one case of mild reactive depression, one alcohol abuser with dementia at age 80 years, and two untreated, possible personality disorders (one described as "nervous" and one as "peculiar" by their general practitioners). Fischer[13] reported pairwise concordance rates for schizophrenia of 48% for MZ and 19% for DZ cotwins. All offspring, including those born out of wedlock, were systematically ascertained and followed up to their latest addresses or

Table 3.—Offspring Distributed by Age at Latest Information (1985) and by Zygosity and Diagnosis of Twin Parent

	No. of Offspring					
	Age, y					
Index Parents	0-14	15-24	25-34	35-44	≥45	Total
Monozygotic Sample						
Schizophrenic twins* (n=11)†	6	1	3	5	32	47
Normal cotwins‡ (n=6)§	1	0	0	0	23	24
Total	7	1	3	5	55	71
Dizygotic Sample						
Schizophrenic twins* (n=10)‖	2	3	0	9	13	27
Normal cotwins‡ (n=20)¶	5	4	10	22	11	52
Total	7	7	10	31	24	79

*Includes schizophrenialike disorders (see text).
†One emigrated female twin with 2 children born and residing abroad is excluded.
‡Includes nonpsychotic disorders (see text).
§One emigrated male twin with 3 children born and residing abroad is excluded.
‖One male twin with 3 illegitimate, untraceable children is excluded.
¶One emigrated female twin with 2 children born and residing abroad is excluded.

to the date of emigration or death. All subjects were followed up through the registers to February 1985. Table 2 shows the important information about the number of reproducing twins by psychiatric status and by zygosity.

The reproductive rate of the schizophrenics (sexes combined) was only 29%, while 64% of the normal cotwins had children. Of those schizophrenics who did reproduce, their average fertility was not different from that of the normal cotwins—3.43 vs 2.89 children. However, the net production of the schizophrenics as a group was below the self-replacement value, at 0.99, while it was 1.84, twice as high, for the normal cotwins. The data for fertility included 10 untraceable children (7 born in the United States and 3 illegitimate children who were not identified).

RESULTS

The twin sample had a total of 150 offspring who could be traced. Table 3 shows the latest information about the age of the offspring by zygosity and the psychiatric status of their parents. Of the 150 children, 14 had "disappeared" from further observation by age 14 years, 10 by death and 4 by emigration. One hundred fifteen (85%) of the remainder were aged 35 years or older, and 58% were past the usual upper limit for the schizophrenia risk period of age 45 years. Little age correction is required for the observed prevalence of schizophrenia in such a sample of offspring as a consequence of the ages of their twin parents.

The offspring of the four groups of twins, schizophrenic and normal identical and schizophrenic and normal fraternal, were compared in two different ways. The first way maximized our sample sizes of parents and offspring; we calculated the morbid risk of schizophrenia in the offspring of all affected twins from both concordant and discordant pairs and compared that risk with the risk for the offspring of unaffected cotwins. We then calculated the risk for offspring of affected twins from *only* discordant pairs and compared that risk with the risk for the offspring of unaffected cotwins. We used two methods for age-correcting the risks, which, in this sample, yielded very similar results: the traditional Strömgren method,[19] with an assumed risk period from 15 to 45 years of age and increasing weights for each 10-year age interval, and the Kaplan-Meier procedure gfrefnum20 for calculating survival experience with respect to age at onset for a diagnosis of schizophrenia. The latter is a nonparametric actuarial method with few assumptions beyond our data on onset ages in relatives and has the advantage of yielding an estimate of the standard errors. Table 4 shows the results for our largest samples.

Table 4.—Schizophrenia and Schizophrenialike Psychosis in Offspring of All Schizophrenic and Normal Twins

	No. of Offspring		
Index Parents	Total	Schizophrenia and Schizophrenialike Psychosis	Morbid Risk, %*
Monozygotic Sample			
Schizophrenic twins (n=11)	47	6	16.8±6.6
Normal cotwins (n=6)	24	4	17.4±7.7†
Dizygotic Sample			
Schizophrenic twins (n=10)	27	4	17.4±7.7
Normal cotwins (n=20)	52	1	2.1±2.1†

*Age correction by the Kaplan-Meier estimate. Values are proportion ± SE.
†$\chi^2 = 2.7947$, $df = 1$,[20] $P<.05$ by unidirectional log-rank test for difference between normal offspring risks.

Table 5.—Schizophrenia and Schizophrenialike Psychosis in Offspring of Only Discordant Schizophrenic and Normal Twins

	No. of Offspring		
	Total	Schizophrenia and Schizophrenialike Psychosis	Morbid Risk, %*
Monozygotic Sample			
Probands (n=3)	14	1	10.0±9.0
Cotwins (n=6)	24	4	17.4±7.7†
Dizygotic Sample			
Probands (n=5)	13	1	8.3±7.6
Cotwins (n=20)	52	1	2.1±2.1†

*Age correction by the Kaplan-Meier estimate. Values are proportion ± SE.
†$\chi^2 = 2.7947$, $df = 1$,[20] $P<.05$ by unidirectional log-rank test for difference between normal offspring risks.

Six secondary cases of *ICD-8* schizophrenia (see Table 7 below) were found among the offspring of the monozygotic schizophrenic twins—three offspring with paranoid schizophrenia, one with catatonic schizophrenia, one with schizoaffective schizophrenia, and one with episodes of schizophreniform psychosis in which he strangled his two children. The estimate (Kaplan-Meier method) of morbid risk is 16.8%. Four secondary cases were found among the offspring of the phenotypically normal MZ cotwins—two offspring with paranoid schizophrenia, one with acute schizophreniform psychosis (*ICD-8* 295.4), and one with schizophrenialike psychosis (*ICD-8* 295.9) who had never been admitted but who had been seen by Fischer during fieldwork (psychotic for 7 years, died at age 47 years of cancer). The morbid risk among the offspring of the normal MZ cotwins is virtually identical, at 17.4%. The corresponding risk figures obtained from the Strömgren method for age correction are 15.5% and 17.4%, respectively.

Turning to the fraternal twins, the offspring risk of the schizophrenic twins was indistinguishable from that of the 2 MZ groups. There were 4 cases, for a morbid risk of 17.4%: 2 offspring with paranoid schizophrenia, 1 with acute schizophreniform psychosis, and 1 suicide by hanging at age 23 years (the general practitioner's statement on the death certificate was severe schizophrenia with auditory hallucinations). Finally, the 52 offspring of the normal DZ cotwins yielded only 1 case, a borderline schizophrenic (*ICD-8* 295.5) who met the criteria for schizotypal personality in *DSM-III-R*, for a morbid risk of 2.1%, much lower than the other 3 groups, and what would be expected for the nieces and nephews of schizophrenic probands.[8] Using the Strömgren method for age correction results in risks of 18.0% and

2.7%, respectively. The important contrast is between the risk for schizophrenia among the offspring of the normal MZ cotwins of schizophrenics, 17.4%, and the risk among the offspring of the normal DZ cotwins of schizophrenics, 2.1%. The difference is significant at the .05 level for the a priori unidirectional test of the unexpressed genotype hypothesis (log-rank test for the comparison of survival curves).[20(p79)] The result supports the contention that discordance in MZ twins is mainly attributable to the unexpression of a genetic liability to schizophrenia rather than to an instance of a nontransmissible phenocopy.

Table 5 presents a different perspective on the data by looking at *only* discordant pairs, reducing the sample sizes for the two schizophrenic proband parent groups. In other words, pairs with both members schizophrenic have been removed from lines 1 and 3, with a consequent reduction in the number of offspring to examine; the data in lines 2 and 4 for the normal cotwins and their children are the same as in Table 4. A twin pair (MZ 9) in which the proband has produced three schizophrenic offspring has been removed, as her cotwin had died at age 18 years, some 17 years before the hospitalization of the proband, casting doubt on the validity of their discordance. The same pattern of resulting morbid risks appears, but the risks to the offspring of schizophrenic twins are reduced by one third to one half of their previous values, although they are still within the confidence intervals expected from Table 4. The apparent reduction in risks is irrelevant to the critical data on the risks for schizophrenia in the offspring of the MZ and DZ discordant normal cotwins, which remain constant across the two methods of data analysis in Tables 4 and 5.

Questions might be raised about whether Fischer's decision to include the offspring from concordant MZ twin pairs together with the offspring of schizophrenic twins from discordant pairs in one group to calculate a risk for the offspring of schizophrenic MZ twins, and the continuance of that practice (Table 4), constitutes an error in data analysis. On the assumption of a polygenic model of some kind for the transmission of schizophrenia, concordant pairs should, other things being equal, have a higher genetic loading, and their offspring should have a higher risk than the offspring of discordant pairs. However, contrary to this expectation, the observed risk in the offspring of normal MZ cotwins in Table 4 is of the same magnitude (17.4% and 16.8%). Such a result appears to strengthen a genetic hypothesis for the etiology of the schizophrenias observed in the offspring of clinically normal MZ cotwins of schizophrenics. The trend toward a lower risk in the offspring of schizophrenics only from MZ discordant pairs, 10.0% in Table 5 vs 16.8% from the "mixture" in Table 4, and a parallel reduction from 17.4% to 8.3% for the fraternal twin schizophrenics support the idea that concordant pairs of twins represent a quantitatively more severe schizophrenia with an increased genetic liability compared with discordant pairs. The data are presented in both ways to highlight both the strengths and the weaknesses of these rare clinical observations.

Calling the discordant twin pairs *discordant* seems to be valid because of their age at last information and the length of follow-up since the proband in such pairs was first admitted to a mental hospital, as shown in Table 6 for the 6 reproductive normal MZ cotwins only. The median age at last information was 64 years compared with age 69 years for the 20 reproductive normal DZ cotwins.

With the possible exception of one spouse with mental retardation and induced psychosis who was married to a fraternal schizophrenic twin, there was no evidence for assortative mating for mental illness, and none of the other twins' spouses were psychotic.

In Table 7 are presented all of the twins' offspring with schizophrenia or schizophrenialike diagnoses divided into the four groups described above, using both their *ICD-8* diagnostic category and their *DSM-III-R* category. Qualitative differences between the two systems in regard to the "true" composition of the category schizophrenia provide food for thought. For some cases in Table 7 it was not possible to determine the precise age of onset of significant schizophrenialike symptomatology prior to hospitalization, as indicated by a question mark. All the case numbers in the table are derived from Fischer.[13]

Other major psychopathologic conditions were seen in only two offspring not mentioned in Table 7: A daughter of a MZ schizophrenic

Table 6.—Age and Length of Follow-up of Discordant Monozygotic Cotwins

Pair No.*/Sex	Cotwin's Age at Last Information, y	Follow-up Time From Proband's 1st Admission, y
6/F	53†	17
26/F	37†	−16
43/M	46†	13
62/F	74†	42
403/F	77†	27
405/M	88†	59
408/M	65	41

*These are the 7 normal, reproducing, monozygotic twins from Table 2. Three children born in the United States could not be traced and were excluded, leaving the 6 discordant monozygotic twins in Tables 4 and 5.
†Dead.

Table 7.—Schizophrenia and Schizophrenialike Disorders in the Offspring of Schizophrenic Twins and Their Normal Cotwins

Twin Parents					Offspring		Diagnosis	
No.	Zygosity*	Sex	Schizophrenic?	Concordant?	Sex	Age at Onset, y	*ICD-8*	*DSM-III-R*
9A	MZ	F	Yes	No†	M	35?	295.7	295.32
					F	39?	295.3	295.32
					F	45?	295.3	295.32
18A	MZ	F	Yes	Yes	F	38?	295.3	295.32
18B	MZ	F	Yes	Yes	F	20?	295.2	295.22
403A	MZ	F	Yes	No	M	33	295.4	295.40
6B	MZ	F	No	...	F	37	295.3	295.32
26B	MZ	F	No	...	M	38	295.3	295.32
43B	MZ	M	No	...	F	35	295.4	295.40
405B	MZ	M	No	...	F	40	295.9	295.92‡
1A	DZ	F	Yes	Yes	M	24	295.4	295.40
1B	DZ	F	Yes	Yes	M	24?	295.3	295.32
					M	30	295.3	295.32
183A	DZ	F	Yes	No	M	21?	295.9	295.90‡
183B	DZ	F	No	...	M	20?	295.5	301.22

*MZ indicates monozygotic; DZ, dizygotic.
†Cotwin died at age 18 years.
‡Provisional diagnosis.

twin (subject 9A) was mentally retarded and unstable and committed suicide at age 37 years, presumably in a state of depression. A son of a DZ normal cotwin (subject 251B) was admitted twice to a mental hospital, at ages 48 and 49 years, for bipolar disorder with full remission; he was 62 years old at last contact.

COMMENT

The data presented from this sample of Danish schizophrenic twins born in the half century between 1870 and 1920, concordant and discordant for schizophrenia, and their adult offspring followed up through the National Psychiatric Register with their parents in 1985 support a strong role for genetic factors, still unspecified, in the etiology of schizophrenia. By the addition of 18 years of follow-up time to Fischer's 1967 observations of her sample,[12] the findings have been confirmed and enlarged. The addition of substantially larger numbers of offspring at risk for schizophrenia has led to more than a doubling of such cases among the offspring, from 6 to 15. The similarity of the results for the age-corrected risks in the MZ offspring between 1967 and 1985 supports the validity of the age-correction procedures in use for genetically conditioned disorders with a variable age of onset.

No support is found for the hypothesis that rearing by a schizophrenic or otherwise psychotic parent is necessary or sufficient for producing schizophrenia in one's offspring.[21] Such a finding complements the results of the American[22] and Scandinavian adoption studies,[23,24] but it does not rule out a role for some other kinds of within-family factors under exploration in a Finnish prospective adoption study.[25] Such factors may serve as releasers or triggers for the genetic diathesis.

Other hypotheses put forward to explain discordance for schizophrenia in identical twins as frequently being due to sporadic cases (newly arisen genetic ones by mutation) or to nongenetic phenocopies caused by putative viruses,[26,27] atrophic disorder with ventricular enlargement,[28] cerebral injuries, intoxications, or diseases[29-31] affecting only one of the pair are not supported by our finding equal risks in the offspring of the sick and the well MZ twins. Such hypotheses do have merit and a place when it comes to explaining the entire panorama of cases that receive a diagnosis of a schizophrenialike disorder at one time or another, but such cases, in the aggregate, are likely to be in the minority in any particular study.[1,32] Again, such factors may of course also act as releasers or as risk-increasing life events.

These ideas can be illustrated with a couple of case histories to make them less abstract. Symptoms of paranoid schizophrenia developed in proband MZ 6A after the birth of her second child at age 25 years. She was admitted to the hospital at age 36 years, where she died at age 53 years following surgery for an abdominal tumor. Except for her father, who committed suicide at age 44 years and was said to have been an alcoholic, the family history is negative. Cotwin 6B also had two children with no psychopathologic consequences; she died at age 53 years following complications of surgery (appendectomy) and was described as completely normal over her life span. The normal cotwin's daughter, unmarried and childless, had five admissions for 2 to 9 months each from age 37 years on because of psychotic episodes with persecutory delusions and third-person auditory hallucinations, at first with almost complete remissions between episodes, later with persistent delusions; this was a clear case of paranoid schizophrenia (her "aunt's" diagnosis). Without this entire scenario, it would have been tempting to invoke childbirth in the life of proband 6A as the cause or as the necessary releaser of her schizophrenia. Doubt is cast on either possibility by the normality of cotwin 6B (she too had two children) and by the onset of schizophrenia in her daughter (whose episodes appeared without any obvious precipitant).

Proband MZ 405A was quite normal, engaged to be married, when at age 23 years he fell onto a stone cornice from 4 m and was unconscious for 5 minutes. He became reserved and increasingly psychotic, with auditory hallucinations and persecutory and bizarre somatic delusions. He was admitted three times to the hospital from age 29 years, for a total of 43 years, with a diagnosis of paranoid schizophrenia. Cotwin 405B married at 19 years of age and had three children; he was steadily employed until retirement, for many years was prone to drinking, but was otherwise normal. From age 80 years he had increasing senile dementia, with admission at age 84 years, until his death at 88 years of a pulmonary embolism. He never had any symptoms to suggest schizophrenia. An insidious psychosis developed in an unmarried daughter at age 40 years, with incoherent speech, preoccupation with spiritualism, and social withdrawal. She lived with her demented father in severe neglect amidst rubbish, decaying food, and human waste until her death at age 47 years from cancer. She was never admitted but was seen by Fischer during her interview in the field with cotwin 405B; the diagnosis was psychosis, possibly schizophrenia. In this scenario the cranial injury appears to have been a sufficient but not a necessary releaser for the predisposition to schizophrenia in proband MZ 405A; the nonschizophrenic cotwin never encountered a releaser for his diathesis but transmitted it to his daughter, whose psychosis had no known precipitant. Without this kind of pedigree, the schizophrenia in the proband might have passed as a nongenetic phenocopy of schizophrenia caused by a cranial insult.

In a design similar to ours, Kringlen[33] had the advantage of using a structured interview (Structured Clinical Interview for *DSM-III*) with the offspring of Norwegian twins. Few details are provided in his preliminary mention of the study. He found similar prevalences of psychopathologic conditions other than schizophrenia in the offspring of the sick and well MZ twins. Among 40 offspring of well cotwins he reported 1 case of *DSM-III* schizophrenia for a prevalence, not an age-corrected risk, of 2.5%, and 1 further case of schizotypal personality, for a total prevalence of 5.0% of "schizophrenia spectrum disorder." Among 25 children of schizophrenic twins 3 were *DSM-III* schizophrenics, for a prevalence of 12%; none were schizotypal, but 2 had paranoid personality disorders. No age correction was used, and we can surmise from the age of the original twin sample[34] that quite a large proportion of their offspring will still be within the risk period for developing schizophrenia in the future. Kringlen did not report on the offspring of his fraternal twins. The numerically higher risks in our Danish sample may be associated with the severity of illness in their parents, although such a relationship with severity is equivocal.[35]

Small samples from the kind of "exotic" design requiring aged offspring of discordant twins limit the robustness but not the provocativeness of the findings. Of the 11 MZ schizophrenic twins with offspring in Table 4, 7 were from discordant pairs, but only 2 were from the *same* pair; the latter (twins 18A and 18B) each contributed 1 schizophrenic offspring to the total of 6 as well as 11 (7 + 4) other nonschizophrenic offspring. Of the 6 normal MZ cotwins in Tables 4 and 5, only 3 (twins 6B, 62B, and 403B) had twin probands who had offspring and could therefore be used in the category in Table 5 of schizophrenic twins only from discordant pairs. Recall that 19 of 31 MZ schizophrenics had no offspring. The validity of the discordance of pair MZ 26 might be questioned, because the "normal" cotwin died at age 37 years, 16 years before the first admission of her sister at age 53 years. The proband twin, however, was increasingly introverted and irritable from age 30 years and was unambiguously psychotic from age 44 years, supporting the evidence for discordance. Considering this pair to be concordant will move 5 grown-up children

with 1 case of schizophrenia from the normal to the schizophrenic index parents groups in Table 4, leading to negligible net changes. Yet another limitation to this study is the inability to detect schizophrenia spectrum disorders below a "caseness" level leading to registration within the Danish system. Cases we might have been able to find by personal interviews should occur with equal rates in the 4 offspring groups and, thus, should only affect the overall level of disorder.

The present study illustrates a phenomenon commonly observed in human genetics, the incomplete expression of a genotype or genetic predisposition (liability) for developing a disease or disorder.[36] The phenomenon is not confined to schizophrenia for psychiatric disorders; we[37] found risks for manic-depressive disorders of 20.7% in the offspring of MZ manic-depressive twins and 24.7% in the offspring of their well MZ cotwins. The corresponding risks for fraternal twins were 14.0% for the offspring of the affected twins and only 2.1% for the offspring of the unaffected cotwins; this is quite close to the rate of 2.6% found for the half-siblings of the entire manic-depressive twin sample of 110 pairs with 414 offspring.

The genotypes for the major psychoses of schizophrenia and manic-depressive disorders can remain completely unexpressed by current clinical criteria, be transmitted, and then be expressed in the next generation, presumably because they encounter a different constellation of putative environmental stressors.[38] Further studies of the unaffected cotwins of psychiatric patients are required to identify putative genetic and biologic markers of mental disorders. The next generation of genetic strategies for unraveling the psychoses must take these data into account.[39-42] To the extent that our findings are valid, they should encourage molecular genetic strategies, as they suggest that phenocopies are infrequent within any one pedigree, increasing the plausability of detecting a major gene variety of schizophrenia under conditions of genetic heterogeneity. Furthermore, the MZ concordance rate may be taken as an estimate of the lower bound of penetrance for linkage studies that assume a single major locus.

Financial support for this work was received from the Scottish Rite Schizophrenia Research Fund, Northern Masonic Jurisdiction; from a fellowship to the Center for Advanced Study in the Behavioral Sciences, Stanford, Calif (Dr Gottesman), underwritten by the University of Virginia, Charlottesville, and the John D. and Catherine T. MacArthur Foundation; and from US Public Health Service grant MH-31302 to Washington University School of Medicine, St Louis, Mo.

We thank our late colleague Margit Fischer, MD, for initiating this project and we dedicate our report to her memory. We also thank Erik Strömgren, MD, and Annelise Dupont, MD, for their encouragement and support, and Daniel R. Hanson, MD, PhD, and Will Grove, PhD, for helpful comments. We thank Sharon Ray and Kit Loll for their aid in the preparation of this manuscript.

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