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Psychiatric Illness in First-Degree Relatives of Patients with Paranoid Psychosis, Schizophrenia and Medical Illness

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This study examines the respective morbid risk for psychiatric illness determined by the family history method in the first-degree relatives of medical controls and patients with delusional disorder (paranoid psychosis) and schizophrenia. The morbid risk for schizophrenia and schizoid-schizotypal personality disorder was significantly greater in the relatives of the schizophrenic patients than in those of the delusional disorder or medical control patients, but no difference in the risk for affective illness or alcoholism was found in the three groups of relatives. Paranoid personality disorder was significantly more common in the relatives of the delusional disorder patients than in those of the medical controls. These results support the familial independence of delusional disorder and schizophrenia.

The nosological status of delusional disorder (or paranoid psychosis) has been a subject of debate since Kraepelin first articulated the modern concept of paranoia in 1896 (Kraepelin, 1902; Lewis, 1970; Kendler & Tsuang, 1981). Three major viewpoints have been expressed on this. The first (e.g. Kolle, 1931; Saken, 1958; Schneider, 1959) is that delusional disorder is a variant of schizophrenia. The second (Specht, 1901) is that delusional disorder is a form of affective illness. The third view, outlined by current diagnostic systems including DSM-III (American Psychiatric Association, 1980), is that delusional disorder is a separate nosological entity, distinct from both schizophrenia and affective illness.

Several empirical methods have been applied to evaluate these three hypotheses, and among the most useful of these has been family studies (Kendler, 1980). We recently reviewed (Kendler & Davis, 1981) six family studies of the frequency of psychiatric illness in the relatives of patients with delusional disorder (Kolle, 1931; Retterstol, 1967; Debray, 1974; Winokur, 1977; Watt *et al*, 1980; Kendler & Hays, 1981). None of these demonstrate an increased frequency of affective illness in the relatives of patients with delusional disorder. Three (Kolle, 1931; Retterstol, 1967; Debray, 1974) suggest a modest increased risk for schizophrenia in relatives of patients with delusional disorder. Two studies have examined the frequency of delusional disorder in relatives of schizophrenic patients (Fisher, 1973; Kendler *et al*, 1981; Kendler *et al*, 1985); one found evidence for an increased risk for delusional disorder in such relatives (Fisher, 1973; Kendler *et al*, 1985) and the other did not (Kendler *et al*, 1981).

All these studies have methodological limitations: out of six, only two contained a comparison group of relatives of schizophrenics (Retterstol, 1967; Kendler & Hays, 1981), and none contained a comparison group of relatives of controls. In only one study was the diagnosis of probands made blind to the status of the relatives (Kendler & Hays, 1981). However in that study, the delusional disorder subjects were not representative of all cases of delusional disorder, since they were retrospectively diagnosed from a group of cases that had previously been considered schizophrenic.

The present study was undertaken in an attempt to replicate the results of previous family studies of delusional disorder. This study attempts to overcome the limitations of previous studies by including prospective identification of patients, a normal and schizophrenic control group, blind diagnoses of probands and relatives, and assessment of 'schizophrenia spectrum' disorders.

Method

Schizophrenic probands were selected using Washington University Criteria (Feighner *et al*, 1971) from consecutive admissions to the Special Treatment Unit at the Bronx Veteran's Administration Medical Center and, depending on the availability of research personnel, from admissions to the general psychiatric unit at the same institution. Control patients were selected from the medical clinics at the same institution. Control probands were excluded from the study if they met Washington University criteria for schizophrenia, affective disorder, or alcoholism.

Delusional disorder probands were selected mainly from the in- and out-patient services of the Bronx Veteran's Administration Medical Center. However, because of the relative rarity of such cases, colleagues at several other

institutions were informed of our interest in such cases. Five such cases were referred to us and were included in this study. In addition, the wife of a patient admitted for major depressive disorder to the Bronx VA was also found to have delusional disorder and was included. The criteria for delusional disorder were similar to those used previously (Kendler *et al*, 1981):

I. Presence of a psychiatric illness of at least one month characterised by the presence of non-bizarre delusions.

II. Absence of (a) prominent affective symptoms sufficient to qualify for the diagnosis of primary affective disorder by Washington University Criteria (Feighner *et al*, 1971); (b) schizophrenic symptoms including: prominent thought disorder (i.e. incoherent speech), bizarre delusions such as thought broadcasting, thought insertion, or delusions of control, marked affective deterioration, and Schneiderian hallucinations (i.e. voices discussing, commenting, or repeating thoughts; (c) clear organic precipitants (i.e. alcohol withdrawal, stimulate use, organic brain disease).

These criteria permit the diagnosis of delusional disorder in cases where secondary depression develops after the onset of the delusional phenomenon. In cases where the proband met criteria for both schizophrenia and delusional disorder, the diagnosis of delusional disorder was given preference. No attempt was made to match the three groups of probands on sex, or demographic or social characteristics. However, 16 out of 18 (88.9%) delusional disorder probands and all the schizophrenic and medically ill control probands were male, and were patients at Veteran's Administration facilities.

Family history evaluations were completed using the Family History Research Diagnostic Criteria (FH-RDC) (Endicott *et al*, 1975) supplemented by family history criteria for 'schizophrenia related personality' developed by the authors (Kendler *et al*, 1984). These criteria were designed to ascertain, by the family history method, two different personality disorders possibly related to schizophrenia: 'schizoid-schizotypal' and 'paranoid'. These two disorders were designed as family history 'equivalents' of two DSM-III personality disorders; schizotypal and paranoid personality disorders. Reliability of the family history raters was tested using the FH-RDC case histories (Andreasen *et al*, 1977). For all raters, the unweighted kappa against the expert's diagnosis exceeded 0.80. Because of the uncertain relationship of paranoid personality disorder to delusional disorder (Stephens *et al*, 1975; Kendler & Gruenberg, 1982), a tentative 'schizophrenia spectrum' was used in this study, which consisted of the diagnoses of schizophrenia and schizoid-schizotypal personality disorder. Paranoid personality disorders were considered as a separate category.

Family history information was obtained using a semi-structured interview from an informant considered by the proband to be best informed about the family. Prior to contact with the informant, the interviewer knew only the name of the proband and the relationship of the informant to the proband, and was therefore blind as to which of the three diagnostic groups the proband belonged. Most interviews were conducted by telephone. At the interviewer's discretion, if insufficient information was obtained from a first informant, other informants could be contacted. If the information available on a relative was inadequate to permit a psychiatric diagnosis or an assignment of no psychiatric diagnosis with at least modest confidence, then the relative was rated as 'no information'.

Previous studies of the family history method have shown that the method has high specificity but is only moderate sensitive (Andreasen *et al*, 1977; Mendlewicz *et al*, 1975; Thompson *et al*, 1982). Therefore, in this study, both probable and definite diagnoses made using the FH-RDC are reported. Probable FH-RDC diagnoses were given when the relative met some, but not all the required criteria, appeared by description to be suffering from the disorder, and was felt to have that disorder rather than any other psychiatric syndrome. Despite the use of these broad criteria, it is likely that the morbid risk for schizophrenia in the relatives of schizophrenics in this study is underestimated.

Probands were asked about their marital status, highest level of education completed, and their personality during childhood and adolescence (i.e. premorbid personality). A normal premorbid personality was characterised by an absence of psychiatric symptoms and normal socialisation patterns. A schizoid premorbid personality was characterised by moderate to severe social withdrawal. Age at onset was defined as the age of the first appearance of psychotic symptoms.

When adequate information was available, all schizophrenic proband were divided into sub-types by the criteria of Tsuang & Winokur (1974). Reliability of the sub-typing was assessed by comparing blindly assigned sub-types after case presentation of the three main raters in this study to that made by the first author (K.S.K.) The number of cases jointly rated and the unweighted kappa for the agreement for the raters were: C.M.—13, 0.86; J.S.—16, 0.77; and R.U.—19, 0.72.

Morbid risk was calculateed using Weinberg's abridged method with an age of risk for schizophrenia, alcoholism, drug use disorder, unspecified functional psychosis, other psychiatric disorder, and schizoid-schizotypal and paranoid personality disorder of 15–39 and for affective illness of 15–59. For anti-social personality disorder, all individuals above age 15 were considered to have completed their age of risk. Statistical analysis was carried out by the student's t-test and the chi-squared test. When expected values in a 2×2 table fell below 1 or the total number fell below 20, a modified exact test was used (Delucchi, 1983; Miettinen, 1974). One-tailed tests were applied for comparisons for which we had a clear expected prediction (e.g. the distribution of schizophrenia and schizoid-schizotypal personality disorder in the relatives of probands with schizophrenia vs. delusional disorder). Otherwise, two-tailed tests were used. All chi-squared analyses are with one degree of freedom. Preliminary results from this project concerning the distribution of psychiatric illness in the relatives of the schizophrenic and control probands have been reported elsewhere (Kendler *et al*, 1984).

Results

Patients and family history evaluations

Sixty-two patients with schizophrenia, 18 with delusional disorder, and 18 medical controls were included in this study. The schizophrenic patients were significantly younger at onset (mean ± SD) (25.1 ± 7.6) than were the delusional disorder patients (38.7 + 15.0) ($t = 3.63$, $df = 78$, $p<.01$), but the ages at evaluation for the two groups did not significantly differ (40.1 ± 12.2 vs. 45.5 ± 12.6, respectively). At evaluation, the medical controls were significantly older (60.7 ± 8.1) than either of the two psychiatric patient groups. The percentage of relatives on whom no information could be gathered was higher in the families of the medical controls (11.1%) than in either the relatives of the delusional disorder (6.5%) or the schizophrenic patients (2.9%). The pattern of the relationship of the primary informant to the proband also differed in the three groups. For the schizophrenic probands, the most common informant was a parent (42.6%), followed by a sibling (41.0%). For the delusional disorder probands, the most common informant was a sibling (44.4%), followed by a spouse (22.2%), or parent (16.7%). For the medical control probands, the most common informant was a sibling (33.3%), followed by either a spouse (27.8%), or a child (27.8%).

Significantly fewer of the schizophrenic (26.7%) than the delusional disorder patients (66.7%) had been married prior to the time of evaluation ($X^2 = 9.62$, $P<.002$). Compared to schizophrenics, patients with delusional disorder tended to be more poorly educated, more frequently non-Caucasian, and more frequently born outside the US. However, none of these differences was statistically significant. A premorbid schizoid personality was significantly more common in patients with schizophrenia (54.2%) than in those with delusional disorder (25.0%) ($X^2 = 4.32$, $P<.05$).

Morbid risk for psychiatric disorders in relatives and families

The morbid risk (MR) for schizophrenia was significantly greater in the relatives of the schizophrenics than in either the relatives of patients with delusional disorder or those of the medical controls (table). Schizoid-schizotypical personality disorder was also significantly more common in relatives of schizophrenic than in relatives of delusional disorder or control probands. When the diagnoses of schizophrenia and schizoid-schizotypal personality disorder were combined into a tentative 'schizophrenia spectrum', the MR for these two disorders was highly significantly greater in the relatives of the schizophrenics (7.2%) than in the relatives of the delusional disorder (0%) or control probands (0%).

By contrast, the MR for paranoid personality disorder was significantly greater in the relatives of patients with delusional disorder (4.8%) than in the relatives of either schizophrenics (0.8%) or medical control probands (0%). No significant differences were found in the MR for affective illness, alcoholism, anti-social personality, drug use disorder, or unspecified functional psychosis in the three groups of relatives. However, a statistically significant excess of other psychiatric disorders was found in the relatives of the schizophrenic probands, compared with those having delusional disorder.

The distribution of psychiatric disorders in the families of the three probands groups was also analysed. The results were similar to those found when analysed by individuals. For example, 30.6% of the families of the schizophrenic probands contained one or more members with a 'schizophrenia spectrum' disorder, compared to 0% of the families of delusional disorder and control probands ($X^2 = 7.09$, $P<.005$ for both comparisons). By contrast, 27.4% of the families of the schizophrenic probands contained one or more members with an affective disorder, compared to 22.2% of the families of the delusional disorder and 27.8% of the families of the medical control patients (all comparisons non-significant).

Paranoid vs non-paranoid schizophrenia

Using the sub-typing criteria of Tsuang & Winokur (1974), sub-type assignment was available for 61 schizophrenic probands. The MR for both schizophrenia and schizoid-schizotypal personality disorder was similar in the two groups of relatives (7.1% and 7.4% in relatives of paranoid and non-paranoid schizophrenics respectively [$X^2 = .01$, N.S.]). Compared to the relatives of patients with delusional disorder, the relatives of patients with paranoid schizophrenia had a significantly elevated MR for schizophrenia ($X^2 = 4.89$, $p<.02$) and for schizophrenia plus schizoid-schizotypal personality disorder ($X^2 = 6.16$, $P<.01$).

Delusional disorder with and without secondary depression

Of the 18 probands with delusional disorder, four met definite and three probable criteria for a secondary depressive syndrome (Feighner *et al*, 1971). The mean age at onset (+ SD) of the probands with definite or probable depression (34.6 + 10.1) did not differ significantly from that found for the remaining delusional disorder probands (41.3 + 17.4) ($t = 0.92$, $df = 16$, N.S.). The only demographic difference found between these two groups of patients was that the proportion of patients with delusional disorder who developed secondary depression and who had at least completed high school (85.7%) was significantly higher than that found for the other delusional disorder patients (30.9%) (modified exact $p<.03$). The risk for affective illness in the relatives of delusional disorder probands with a definite or probable secondary depression (0/21.5) was lower than that found in delusional disorder patients without a secondary depression (4/48.5 = 8.2%), but this difference was not statistically significant ($X^2 = 1.73$, N.S.).

Discussion

The purpose of this study was to clarify from a familial perspective the relationship between delusional disorder and schizophrenia. As demonstrated previously (Stephens *et al*, 1975; Kety *et al*, 1975;

TABLE

The morbid risk for psychiatric disorders as determined by family history in the first-degree relatives of probands with schizophrenia, delusional disorder and medical illness

Relatives	Proband diagnosis: Schizophrenia	Delusional disorder	Medical control
N	330	100	119
BZ 15–39	264	84	101
BZ 15–59	204	70	80.5
		Psychiatric disorders	
Schizophrenia—N	8	0	0
MR	3.0	—	—
SSPD—N	11	0	0
MR	4.2	—	—
Schiz + SSPD—N	19	0	0
MR	7.2	—	—
PPD—N	2	4	0
Affective illness—N	21	4	7
MR	10.3	5.7	8.7
Alcoholism—N	18	8	5
MR	6.8	9.5	5.0
Antisocial personality—N	3	1	0
MR	0.9	1.0	—
Drug use disorder—N	1	0	1
MR	0.4	—	1.0
Unspecified functional psychosis—N	1	0	0
MR	0.4	—	—
Other disorder—N	21	1	4
MR	7.9	1.2	4.0

Psychiatric disorder	Statistical analysis: Morbid risk in relatives of probands with: Schizophrenia vs delusional disorder	Schizophrenia vs control	Delusional disorder vs control
Schizophrenia	.05	.04	NS
SSPD	.03	.02	NS
Schizophrenia + SSPD	.006	.003	NS
PPD	.01	NS*	.03
Affective illness	NS	NS	NS
Alcoholism	NS	NS	NS
Antisocial personality	NS*	NS*	NS*
Drug use disorder	NS*	NS*	NS*
Other disorder	.03	NS	NS

* By modified exact test, otherwise by X^2.

Abbreviations: SSPD—schizoid-schizotypal personality disorder; PPD—paranoid personality disorder; BZ—bezugsziffer of life-times of risk; MR—morbid risk.

Kendler *et al*, 1981; Lowing *et al*, 1983), the risk for both schizophrenia and schizoid or schizotypal personality disorder is elevated in relatives of schizophrenic patients. If delusional disorder was a sub-type of schizophrenia, these disorders should also aggregate in families of patients with delusional disorder. However, this was not observed in the present study. The morbid risk (MR) for both schizophrenia and schizoid-schizotypal personality disorder in the relatives of delusional disorder patients did not differ from that found in the relative of controls, and was significantly lower than that found in the relatives of schizophrenics. The analysis of these results by families indicates that the differences found in the analysis of relatives was not due to many psychiatric cases clustering in a very few families.

Although the sample size was not large, some demographic differences between the delusional disorder and schizophrenic probands were found. Consistent with previous findings (Kendler, 1982), patients with delusional disorder were significantly older at onset than were the schizophrenics. A significantly greater percentage of patients with

delusional disorder than schizophrenia had been married prior to evaluation. This difference was not due to differences in age at evaluation, since this did not differ significantly in the two groups. As has been noted previously (Kendler, 1980), a schizoid premorbid personality was much more common in the schizophrenic than in the delusional disorder patients. Our previous review noted that compared with patients with schizophrenia, patients with delusional disorder were more likely to be immigrants and to come from more socially disadvantaged backgrounds (Kendler, 1982). Although not statistically significant, the trends in this study were also in that direction.

It has been suggested that delusional psychoses can be placed on a continuum from non-paranoid schizophrenia at one extreme to 'paranoia' or delusional disorder at the other. In this model, paranoid schizophrenia occupies an intermediate position (Magaro, 1981; Munro, 1982). The validity of this hypothesis is testable from a familial perspective, and predicts that the risk for 'schizophrenia spectrum' disorders in the relatives of paranoid schizophrenics should be intermediate between that found in the relatives of non-paranoid schizophrenics and patients with delusional disorder. However, such a pattern was not observed in this report. The results of this study do not support the validity of a continuum model for delusional psychoses, but rather suggest that paranoid and non-paranoid schizophrenia share familial factors that appear to play little role in the pathogenesis of delusional disorder.

The risk for affective illness is substantially greater in relatives of patients with affective illness than in those of controls (Gershon *et al*, 1976). If delusional disorder was a sub-type of affective illness, the risk for affective illness in relatives of delusional disorder probands ought to substantially exceed that found in the relatives of controls. However, in this investigation, the MR for affective illness did not significantly differ in the relatives of patients with delusional disorder and control patients respectively. These results are not consistent with the hypothesis that delusional disorder is aetiologically related to affective illness.

The family history method has been demonstrated by others (Andreasen *et al*, 1977; Winokur *et al*, 1972) to detect the familial aggregation of affective illness. However, in this study, no group of affectively ill probands was included, so that the possibility cannot be ruled out that in our hands, the method was insensitive at detecting affective illness. However, this is unlikely for two reasons. Firstly, the MR for affective illness in the relatives of schizophrenics is similar to that detected previously, using the family history method (Winokur *et al*, 1972), suggesting that affective illness was being detected at a normal rate in these relatives. Secondly, during the time this study was being conducted, a small-scale family history study of affective illness was being undertaken at the same institutions. Although non-blind, the raters in that study were also trained in the FH-RDC criteria by the senior author (K.S.K.) To date, the MR for affective disorder in their relatives is 18.3%, a rate similar to that found by others in relatives of affectively ill patients using the family history method (Andreasen *et al*, 1977; Winokur *et al*, 1972). This rate is significantly higher than that found in the relatives of patients with delusional disorder ($X^2 = 5.27$, $P < .02$).

Whilst affective illness, when considered as a uniform entity, does not appear to be related to delusional disorder, a significant sub-group of patients with delusional disorder may have a disorder aetiologically related to affective illness. In this sample, patients with delusional disorder frequently developed secondary depression. Perhaps these are the cases of delusional disorder who are aetiologically related to affective illness. However, the family history data do not support such a hypothesis: the MR for affective illness did not significantly differ in relatives of delusional disorder patients with and without secondary depression. As with previous studies, the present results do not support the view that delusional disorder is closely related aetiologically to affective illness.

Since paranoid personality disorder shares several clinical features with delusional disorder, clinical intuition suggests that these two disorders might be aetiologically related. However, the only family studies undertaken to date have examined the relationship between paranoid personality disorder and schizophrenia; both have suggested a modest familial link between the two disorders (Stephens *et al*, 1975; Kendler & Gruenberg, 1982). In this present study, a slight and non-significant excess of cases of paranoid personality disorder was found in the relatives of schizophrenics versus controls. However, the MR for paranoid personality disorder was significantly higher in the relatives of the delusional disorder probands, compared to either the relatives of the schizophrenics or the controls. These results suggest that the familial link between paranoid personality disorder and delusional disorder is stronger than the link between paranoid personality disorder and schizophrenia.

The definition of delusional disorder used here is similar to, but not identical with the criteria for paranoid disorder proposed in the DSM-III. There are two major differences in the two sets of criteria. Firstly, the criteria for delusional disorder permit any kind of delusion, while those for paranoid disorder restrict the kind of delusion to those with persecutory or jealous themes. Secondly, the criteria for delusional disorder permit auditory hallucinations as long as they are not 'Schneiderian' in nature (i.e. voice discussing, commenting or repeating thoughts), while the DSM-III criteria require 'no prominent hallucinations'. Of the 18 probands with delusional disorder examined in this report, 13 clearly met DSM-III criteria for paranoid disorder. Comparing the demographic characteristics of the five cases who probably did not meet the DSM-III criteria with the 13 who did, the only difference found was their age at onset. The former had a mean (+SD) of 25.2+8.2, while for the latter, the mean was 43.8+13.9 ($t=2.78$, $df=16$, $P<.01$). No difference was found in the MR for psychiatric disorders in the relatives of these two groups of delusional disorder probands. Although based on a small number of cases, these results do not suggest any major differences between those patients meeting the criteria for both delusional disorder and DSM-III paranoid disorder and those meeting only criteria for delusional disorder.

Psychiatric illness in the relatives of probands in this study was ascertained by the family history method. Compared to the family study method, which involves direct interviews with relatives, it has high specificity but only moderate sensitivity (Andreasen *et al*, 1977; Mendlewicz *et al*, 1975; Thompson *et al*, 1982). However, the results of this investigation depend on the comparison of MRs for psychiatric disorders in the relatives of three proband groups, not on the absolute MRs found. Therefore, the results of this study would be valid as long as the sensitivity of the family history method did not substantially differ in the three groups of relatives. While differences in sensitivity of this method in the three groups of relatives could not plausibly be due to the raters, who were blind to the status of the proband, it cannot be ruled out that the informants for the three groups of relatives might have differed in their 'threshold' for reporting psychopathology in their families. For example, the informants for the control probands might have had a higher threshold for reporting psychopathology than the other informants. However, the rates for affective illness and alcoholism in the families of the control probands were very similar to that found in the families of the schizophrenic and delusional disorder probands. These results suggest that the relatives of controls did not have a general bias toward under-reporting psychopathology, compared to the relatives of the psychiatrically ill probands. However, it remains possible that part of the excess of the 'schizophrenia spectrum' disorders in the families of the schizophrenics resulted from a greater ability or willingness in relatives of schizphrenics to recognise such psychopathology in their relatives.

The percentage of relatives about whom insufficient information was available differed in the families of the schizophrenic and medical control probands respectively. This finding probably resulted from differences in age at evaluation of these probands. Of the 15 relatives of controls about whom insufficient information was available, 11 (73.3%) were parents, most of whom had died more than three decades prior to the study. Of the ten relatives of schizophrenics about whom insufficient information was available, only three (30.0%) were parents. Given the small number of cases involved, the differences in completeness of ascertainment in the three groups of relatives probably did not substantially alter the results obtained.

A final potential deficiency in the family history evaluations in this study was that the pattern of the relationship of the informant to the proband differed in the three groups of probands. Since the informant suggested by the proband to know most about their relatives was the one contacted, these differences presumably emerged from differences in the structure of the three groups of families. The medical control patients, with a mean age of about 60, had few living parents, but frequently had children. With their low rate of marriage and diminished fertility, the schizophrenics infrequently had either spouses or children as informants. What possible bias could have been introduced by the different pattern of informants used in the three proband groups? In a thorough evaluation of the family history method, Thompson *et al* (1982) examined the sensitivity and specificity of the psychiatric diagnoses provided by parents, siblings, spouses, and offspring. They found that all four kinds of informants provided family history data that had a high specificity. However, the sensitivity of the family history information given by spouses and offspring was higher than that given by parents and siblings. The percentage of informants who were spouses or offspring for the three proband groups were: controls—58.6%, delusional disorder—27.8%, schizophrenics—1.7%. Therefore,

according to Thompson *et al*, any bias introduced by differences in the patterns of informants in the three proband groups would tend to diminish rather than exaggerate the differences found.

The results of this investigation support the hypothesis that, from a familial perspective, delusional disorder is closely related to neither schizophrenia nor affective illness. This study does not support the hypothesis that paranoid schizophrenia can be placed on a continuum between delusional disorder and non-paranoid schizophrenia. Finally, results from this study suggest that paranoid personality disorder may have a stronger familial link to delusional disorder than to schizophrenia.

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