

JASON SCHIFFMAN, AMY ABRAHAMSON,
TYRONE CANNON, JOSEPH LABRIE, JOSEPH PARNAS,
FINI SCHULSINGER, AND SARNOFF MEDNICK

Early Rearing Factors in Schizophrenia

There are mixed findings in research on the relationship between risk of developing schizophrenia and early rearing factors such as family dysfunction and parental loss or separation. These relationships, however, seem clearer when the vulnerability resulting from a genetic liability to schizophrenia is taken into consideration. It appears that when combined with genetic risk for schizophrenia, disruptive early rearing circumstances contribute significantly to later schizophrenic outcome.

We begin our review of the literature on early rearing and schizophrenia by looking at studies in which the parents of subjects are not selected for mental illness; in these studies, genetic liability for schizophrenia is not taken into consideration. Following this, we review research of early rearing circumstances of children with mental illness in the family. Children with a family history of schizophrenia may have an important vulnerability that interacts with poor early life circumstances and increases the likelihood of later schizophrenia.

Family disharmony and schizophrenia: Low-risk studies

There has been no shortage of theories to explain the relationship between family dysfunction and schizophrenia in offspring. Most of these theories have been psychoanalytic [1]. There have, however, been few empirical investigations of these theories. Some of the studies that do exist suffer from methodological shortcomings. Common research critiques include: inadequate control groups, small sample

Jason Schiffman, Amy Abrahamson, Tyrone Cannon, and Joseph LaBrie are associated with the University of Southern California, Los Angeles, CA; Joseph Parnas and Fini Schulsinger, with the Institute of Preventive Medicine, Copenhagen Hospital Corporation, 1399 Copenhagen, Denmark; and Sarnoff Mednick, with the Social Science Research Institute, University of Southern California, and the Institute of Preventive Medicine, Copenhagen, Denmark.

sizes, inconsistent operationalization of “family dysfunction,” failure to include possible confounding factors, and retrospective bias. In addition, the studies that have been published have not lent strong support to the theories (e.g., [2]). In light of the limited number of studies, methodological limitations, and mixed findings, Roff & Knight [3] suggest that the etiological significance of family functioning to schizophrenia is unknown.

The University of California at Los Angeles (UCLA) Family Project [4] attempted to overcome some of the methodological limitations of previous research investigating family influence on schizophrenia. Goldstein [4] theorized that various dysfunctional methods of communicating contributed to the development of schizophrenia. In this study, family dysfunction was consistently operationalized, and data were gathered prospectively. The project, however, did not select subjects based on a genetic vulnerability.

The UCLA Family Project of family functioning and schizophrenia followed the families of disturbed adolescents before the onset of major psychopathology [4]. The purpose of the study was to identify behaviors in parents associated with later schizophrenia in their children before the children became schizophrenic. Affective style (affective attitudes that are negative, critical, intrusive, or guilt-inducing) and communication deviance (inability of a parent to establish and maintain a shared focus with the teenager) were investigated. Conclusions from the study are limited by the very small number of subjects. Goldstein [4] reports that a combination of high parental communication deviance and negative affective style did not produce what was a narrowly defined conception of schizophrenia spectrum disorders in the offspring.

The UCLA results became more informative when family history of psychopathology was investigated. Seventy-one percent (five of seven) of subjects with both a positive family history of severe psychopathology and high communication deviance later manifested a narrowly defined spectrum disorder. Of subjects with a negative family history for severe psychopathology and low communication deviance, only 20 percent (one of five) later manifested a narrowly defined spectrum disorder. Goldstein concludes: “However one interprets these data, they do point to an important combination of predictors (family history of severe psychopathology and high communication deviance)” [4].

These findings support the notion that a family history of psychopathology and unsatisfactory family functioning interact to contribute to the development of schizophrenia. This presumed interaction suggests a vulnerability–stress model of schizophrenia, to be described in more detail below.

Parental loss and schizophrenia

Numerous studies examine parental loss and the development of general psychopathology, and of schizophrenia specifically. Granville-Grossman [5] reviewed 13 studies, conducted between 1943 and 1963, of parental death in childhood and

schizophrenia. Of these studies, eight reported elevated rates of losing at least one parent among patients with schizophrenia (e.g., [6,7]). The remaining five reported no significant increases in the frequency of parental death among children under the age of 18 who later developed schizophrenia. More recently, Ragan & McGlashan [8] noted mixed findings from investigations of parental absence and schizophrenia. In their own study [8], they failed to detect a significant relationship between early parental death and later schizophrenia. Many of the studies included in these investigations suffer from methodological limitations that may have influenced the findings. Common critiques of parental loss studies include: poorly defined samples, reliance on old records, lack of systematic data, inadequate control groups, various types of loss, and various ages at which separation occurred.

Whether parental loss serves as a general risk factor for later mental/emotional problems, or whether such an experience has a specific impact on schizophrenia as an outcome, is another issue researchers have attempted to address. Hilgard & Newman [9] report a higher incidence of early parental death in schizophrenic patients compared with a nonpsychiatric control group; the schizophrenia group did not, however, differ from alcoholic patients. A study by Gay & Tonge [10] found higher rates of parental absence in people with reactive depression than in people with schizophrenia. Munro & Griffiths [11] suggest a greater rate of parental absence in depressed patients than in schizophrenic patients and matched controls, between whom there was no significant difference. Finally, Ragan & McGlashan [8] failed to find a significant difference in the rate of parental loss among eight nonoverlapping diagnostic groups, including schizophrenia. Overall, conclusions are not clear (and are often negative) regarding the specific effects of separation on schizophrenia as an outcome.

As noted above, studies of parental loss and schizophrenia do not reveal a clear relationship. Therefore, researchers have attempted to identify possible moderators of the relationship between parental loss and schizophrenia. Such factors include the type of separation and the age at which separation occurs.

The effects of different types of parental loss are an important area of interest. The majority of studies of parental loss consider only loss through death. Parental separation through divorce, however, may have a unique effect on child development. Family circumstances surrounding parental separation are often different from circumstances surrounding parental death. Gay & Tonge [10] investigated the relationship between various mental disorders and parental absence through death or separation. Unfortunately for our purposes, the study contained data for only six persons with schizophrenia and were collected retrospectively. Pitts and colleagues (cited in [11]) found no association between schizophrenia and parental divorce or death. Brill & Liston [12] did find an increase in parental divorce or separation, but not an increase in parental death, among persons with schizophrenia. More recently, Furukawa and colleagues [13] investigated the rate of early parental death or separation in 218 persons with schizophrenia; there was no sig-

nificant relationship between the early death or separation of a parent and later schizophrenic outcome in the child. Maekikyroe and colleagues [14] reported no significant increase in later schizophrenic outcome among persons reared in one-parent families (mainly through divorce) compared with two-parent families.

Findings are inconclusive regarding the relationship between type of loss and later schizophrenia. Age at separation is another important factor that may mediate the relationship between schizophrenia and early parental absence. Children at different developmental stages may have differing levels of vulnerability to stress associated with parental loss. The above-reviewed studies generally consider early parental loss to include loss before the ages of 16 to 19. Hilgard & Newman [9] specifically addressed the issue of age at separation. Their study examined the siblings of patients with schizophrenia who had lost a parent: overall, the age at loss among the patients did not differ significantly from that of the nonaffected siblings. Thus, in that study, age during childhood at which a parent was lost did not significantly relate to later schizophrenia, and the authors conclude that parental loss is not related to later schizophrenia.

Watt & Nicholi [15], however, did find an association between early parental death and later schizophrenia. The average age when a parent was lost for persons with schizophrenia in two samples was 6.8 and 5.3 years. These subjects were two years younger at the time of loss than were the nonschizophrenic, well-matched controls—in other words, younger children suffering parental loss were more likely to decompensate into schizophrenia than children just two years older. Like other studies of parental loss and schizophrenia, studies of age at separation have yielded mixed results.

Studies of vulnerable children

The above reviews reveal no consistent pattern of findings regarding the relationship between early negative life events and schizophrenia, and investigations of some possible moderators do not clarify the relationship. There is, however, one group of studies examining family-rearing stress effects on schizophrenic outcome that has noted consistently significant effects. These studies consider rearing stress in samples of vulnerable children. In most cases the children are defined as vulnerable (“high risk” or “HR”) because they have a parent with schizophrenia.

Family disharmony and schizophrenia: High-risk studies

Some research (discussed below) has linked stressful family environments with later development of schizophrenia in HR children. Many questions regarding the direction of effects remain (e.g., Does a poor family relationship have a later impact on a child, or does a disturbed child already on a trajectory toward schizophrenia have a negative impact on the family?). Several theories, however, impli-

cate family functioning as a causal factor in schizophrenia in genetically at-risk persons. For example, Gottesman [16] speculates that stress (such as a disharmonious family environment) “may operate only on the relatively few genetically predisposed individuals near the threshold for overt illness and have little or no effect as independent causes of schizophrenia in the general population.” Based on a review of family relations research pertaining to schizophrenia, Asarnow [17] concludes that evidence “points to the highest rates of schizophrenia spectrum disorders in individuals exposed to both disturbed rearing environments and genetic risk.”

In an effort to identify factors involved in the etiology of schizophrenia, Mednick & Schulsinger [18], in 1962, began the Copenhagen High Risk Project. The project was a longitudinal study of 207 offspring of mothers with schizophrenia and a low-risk comparison group of 104 children. When the study was initiated, none of the participants met criteria for any psychiatric diagnosis.

In this project, Talovic¹ reported that HR children with socially unstable mothers were at increased risk for schizophrenia. Maternal characteristics were determined by hospital records and a psychiatric interview, and qualities such as preschizophrenia antisocial tendencies, sexual promiscuity, substance abuse, and unreliable employment history in the mother were coded.

Two other reports from this project [19]² suggest that HR children who later developed schizophrenia reported less satisfactory relationships with their parents than those who did not. Parent-child relationships were assessed during interviews of both the parents and the child by a social worker and a psychiatrist. The average age of the children was 15.1 years old. The parent-child relationship scales contained items that related to the children's attitudes toward their mothers and fathers, the nature of the relationship as perceived by the parents, and the current frequency of contact. Results suggest that getting along well with both parents may protect HR children from decompensation, whereas not getting along with both parents may increase the likelihood of developing schizophrenia.

It is possible that in this study unfavorable infant attributes might have been responsible for the poor family relationships, as the stress of having a child who behaves badly may disrupt parent-child relations. Also, unfavorable attributes in infancy may be an early sign of later decompensation into schizophrenia. From this perspective, it is not poor parental relations that cause later schizophrenia; rather, it is early signs of schizophrenia that cause poor parental relations.

Infant characteristics of attention span, passivity, stubbornness, and temperament were assessed retrospectively at the time of the first assessment in 1962. Analyses failed to detect a significant association between infant characteristics and later adequacy of parent-child relationships. This finding does not support the hypothesis that unfavorable early attributes of the preschizophrenic child negatively affect perception of parental relationships.

In order better to study perinatal factors, Mednick and colleagues [20] then initiated the Danish Perinatal HR Project, a second longitudinal study of a group

of children with schizophrenic parents. Subjects were drawn from a Danish birth cohort consisting of all children born between 1 September 1959 and 31 December 1961 at Rigshospitalet in Copenhagen [21]. The cohort consisted of 9,125 subjects from consecutive deliveries for whom prenatal and perinatal data were available.

In 1972, a sample of 265 children from this cohort was intensively examined [20]. All children with one parent with a psychiatric registry diagnosis of schizophrenia comprised the HR group ($N = 72$). A group of matched controls (consisting also of 72 children) had parents with recorded psychiatric diagnoses other than schizophrenia. The remaining 121 subjects were matched controls with no parental records of psychiatric hospitalization. Both control groups were well matched with the high-risk birth cohort [20].

Measures of family environment were gathered by a social worker when the children were 11 years of age. The questions included father's attitude toward the child, mother's attitude toward the child, social-class rating, living conditions, and the child's opinion of the family. In this project, the families of high-risk subjects who later decompensated to schizophrenia reported more stressful family characteristics in childhood than the families of subjects who did not develop schizophrenia.³ This pattern was not found in the families of low-risk subjects.

Results from another longitudinal high-risk study suggest an association between poor parenting and later schizophrenia in children whose parents have schizophrenia. In the NIH Israeli Kibbutz–City Study, Marcus and colleagues [22] reported an association between inconsistent parenting, overinvolvement, and hostility toward the child and later schizophrenia-spectrum decompensation in children whose parents had schizophrenia (schizophrenia, $N = 5$; schizoid personality disorder, $N = 3$; “mixed spectrum” disorder, $N = 1$). It should be noted that the number of subjects in this study was limited.

The above studies support the interactive relationship between family dysfunction and the resulting high risk that impacts on later schizophrenia. Another interpretation of these results suggests that mothers and fathers who have poor relationships with their children may also have a greater genetic liability for schizophrenia: a high genetic contribution may adversely affect the family relationship. Furthermore, the elevated genetic contribution may increase the risk for schizophrenia in the offspring independently of family relations. This interpretation predicts that high genetic liability will be associated with unsatisfactory family relations. In this alternative model, family relations are not causally related to the later diagnostic outcome of the offspring: instead, this outcome is associated with having parents with high genetic loading.⁴

An adoption study by Tienari [23] indicates that poor family relationships contribute to risk of schizophrenia in the offspring of parents with schizophrenia. This study found that HR offspring are more likely to develop psychopathology when placed in a disturbed adoptive family than when placed in a healthy adoptive family. The findings from this investigation support the hypothesis that a positive

family rearing environment can protect genetically vulnerable children from future psychosis.

High-risk studies of parental loss and schizophrenia

Accounting for genetic liability for schizophrenia may help explain the previously reported equivocal relationships between schizophrenia and parental absence [24,25]. Studies directing attention to persons genetically vulnerable to schizophrenia who suffer parental absence reveal a more consistent relationship than studies failing to incorporate genetic risk.

In the Copenhagen High Risk Project, children who experienced maternal and paternal separation because they were institutionalized (but not in supportive foster homes) during the first three years of life were more likely later to develop schizophrenia. (In this study, institutional placement was defined as placement in a nonfamilial child-care institution for at least six consecutive months at any time during the child's first three years of life.) This relationship was not found among children who did not have a parent with schizophrenia. Possible confounding factors, such as severity of the genetic loading parents transmitted to offspring and infant characteristics, were investigated to determine if other factors besides institutionalization were responsible for later schizophrenia. After controlling for these confounding factors, early institutionalization remained a significant predictor of later schizophrenia.

Data from the Danish Perinatal HR Project suggest an increased risk for schizophrenia among HR children who were separated from their parents in infancy. In the Danish perinatal cohort of 9,125 children, elevated levels of separation during the first year of life were associated with increased risk for schizophrenia in those with a family history of schizophrenia.⁵ As the authors point out, this finding should be viewed with caution since there are confounding factors that limit the interpretations. Most notably, separation in the first year is also a good predictor of later childhood experiences of parental separation and disrupted rearing (the mother has more marriages, the mother tends not to be married to the father, the child has little contact with the biological father, the child experiences more full-time day care). It may be that the family stress critical for the development of schizophrenia occurs later in life. Early separation may be only a sign of a later harmful, unstable environment.

Rate estimates of persons with early family discord or parental separation who later develop schizophrenia

Varying techniques in the assessment of family functioning make it difficult to estimate the impact of disruptive family experiences on later schizophrenic development.⁶ Based on two prospective studies, however, the relationship between negative family conditions and child psychiatric outcome can be estimated. It should

be stressed that in both studies, the quality of parental relationships was assessed before the onset of schizophrenia.

In the kibbutz study [22], 9 of 50 high-risk subjects had schizophrenic outcomes. Of those who decompensated into schizophrenia, all nine were considered to have had poor parenting. Of the 50 high-risk subjects, 16 (32 percent) had poor parenting. Of the high-risk subjects who had poor parenting, 56 percent (9) were later diagnosed with a schizophrenia spectrum disorder (schizophrenia, $N = 5$; schizoid personality disorder, $N = 3$; "mixed spectrum" disorder, $N = 1$). Finally, in this study no high-risk subjects with good parenting later developed schizophrenia.

In the Copenhagen High Risk Project, of 207 high-risk subjects, 47 had parental relationships perceived as poor. Of those 47 subjects, 11 (23.4 percent) later developed schizophrenia. Only 4 of 57 (7.0 percent) of the high-risk subjects with good parental relationships developed schizophrenia. In this high-risk sample, the likelihood of developing schizophrenia was more than three times greater among subjects with family relationships perceived as poor compared with subjects reporting positive family relationships.

Data from the Copenhagen High Risk Project and the Danish Perinatal Project can provide estimates of the risk for schizophrenia in HR subjects separated from their parents. In the 1962 Copenhagen study of children with schizophrenic mothers, early separation (up to the age of three) was associated with later schizophrenia in the children. Thirty-three percent (9/27) of the high-risk subjects separated during the first three years of life decompensated to schizophrenia, whereas only 12 percent (22/180) of high-risk children not separated from their family during their first three years decompensated. Subjects who experienced early separation from their family were almost three times as likely to develop schizophrenia as subjects who did not suffer separation.

The data from the Danish Perinatal cohort provide an opportunity to examine prevalence rates based on a complete population of children. Unfortunately, the measure of separation from parents is limited to information on the first year of life. In the total sample, 59 of 7,792 (0.8 percent) subjects not separated from their family in the first year developed schizophrenia, whereas 14 of 607 (2.3 percent) who were separated in the first year did develop schizophrenia (almost a threefold difference). Of the above-mentioned 14 subjects separated who later manifested schizophrenia, 12 were at high risk. Eighty-three percent (12 of 14) of separated persons who later develop schizophrenia are at high genetic risk. In this sample, the HR subjects account for the increased rate of schizophrenia (2.3 percent vs. 0.8 percent) found among separated children in the entire population. Thus, separation is primarily predictive of later schizophrenia in children at genetic risk for schizophrenia. It is possible that the mixed findings concerning absence of the family and later development of schizophrenia may be due to failure to account for genetic risk for the disorder.

Among high-risk subjects, 16.7 percent (12 of 72) were separated from their

family and developed schizophrenia, whereas only 4.2 percent (3 of 72) of high-risk subjects who remained with their family developed schizophrenia. The rate of schizophrenia among high-risk subjects who were separated is significantly greater than the rate of schizophrenia among high-risk persons who were not separated from their families. Thus, among at-risk subjects, separation from the family increases the rate of later schizophrenia.

The two-hit theory

The above findings suggest that the likelihood of developing schizophrenia is increased by an interaction between early childhood stress and a genetic liability to schizophrenia. We have proposed a “two-hit model” to help explain this interaction [26]. The two-hit model suggests that two events, or “hits,” are associated with increased risk for schizophrenia. The first hit can stem from a genetic liability for schizophrenia. It is hypothesized that this genetic liability may be transmitted from a parent with schizophrenia, and may result in a preprogrammed disruption of fetal neural development. The disruption of fetal neural development may interfere with neural migration, connections, or cell death, and may be associated with later cognitive and perceptual disturbances. These disturbances may later increase the risk for psychological decompensation.

Neural developmental disruption can also be caused by events during gestation. These prenatal events (potential first hits) might include maternal influenza or maternal stress during a critical period of gestation (e.g., second trimester) [26]. Examinations of this model, however, have generally focused on having a parent with schizophrenia as the indication of a first hit (for a summary, see [26]).

The second hit takes the form of an environmental stressor. Possible second hits include delivery complications, separation from parents, institutional rearing, and high levels of family stress. According to the theory, in the absence of a first hit, a second hit does not increase the risk for schizophrenia; in conjunction with a first hit, however, a second hit increases the likelihood of later schizophrenia [27].⁷ Therefore, investigations into the impact of early childhood rearing (second hits) on later schizophrenic outcome may be more informative if they include people likely to have experienced a first hit.

Prevention

Identifying children at risk for a first hit

The above findings have implications for primary prevention. As indicated, the impact of negative rearing circumstances on later schizophrenia seems dependent on the occurrence of a first hit. Identification of subjects at risk for a first hit, therefore, is critical for any primary prevention targeting early childhood experiences.

As noted above, a reliable method of identifying persons at risk for a first hit is to assess parents for a history of schizophrenia. Approximately two-thirds of mothers with schizophrenia, however, are given a psychiatric diagnosis *after* the birth of their children, i.e., maternal diagnosis may come after a time that would be critical for perinatal intervention or early intervention in family functioning. Specifically, children may be institutionalized before age three or experience separation during the first year of life, before they are identified as being at high risk for developing schizophrenia. Identifying mental disorders in pregnant women, however, could be improved through programs educating medical care providers regarding early signs of mental illness.

Previous research has uncovered other risk factors for first hits that may help identify people at risk for schizophrenia [28].⁸ Several studies suggest a relationship between prenatal exposure to influenza during the second trimester of gestation and later development of schizophrenia [28–31]. That relationship may mimic the teratogenic effects of disruption of genetic fetal neural development. If a mother suffered a second-trimester influenza infection, assessment (and perhaps treatment) of the child may be offered.

In addition to influenza infection, recent research suggests that the stress of experiencing a natural disaster while pregnant may also mimic the effects of disruption of genetic fetal neural development. Preliminary results by Kinney and colleagues suggest a link between mothers affected by a tornado in Massachusetts during the second trimester of pregnancy and schizophrenia in offspring.⁹

Researchers find an increase in minor physical anomalies (MPAs) in patients with schizophrenia [32]. MPAs are slight deviations in external physical characteristics (e.g., high-steeped palate, large or small distance between tear ducts, adherent earlobes). These deviations may be possible markers of a first hit. MPAs are thought to occur during periods of abnormal central nervous system development [33,34]; they can signify any type of developmental disruption triggered by genetics, influenza, or other types of first hits. The presence of MPAs does not always signal the occurrence of a schizophrenia-relevant first hit, as MPAs may result from a disruption occurring during a fetal period not critical for the development of schizophrenia (e.g., first or third trimester of pregnancy). MPAs do, however, signify an increased risk of a person's having experienced a first hit.

The presence of MPAs may be a valuable tool for recognizing low-genetic-risk people at elevated risk for schizophrenia. Schiffman and colleagues¹⁰ report an interaction between MPAs (indicator of a first hit) and an unstable rearing environment (second hit) predicting a schizophrenic outcome in low-genetic-risk subjects. MPA assessment is easy and reliable, and can be used by health professionals to identify children at risk for later schizophrenia. Early identification of these vulnerable children may be invaluable in targeting those who may benefit from primary prevention programs. It should be noted, however, that using MPAs alone as a "predictor" of schizophrenia results in many false positives.

Interventions directed toward early childhood rearing

The evidence reviewed suggests that parental absence and poor family environments predict schizophrenia in people who have experienced a schizophrenia-relevant first hit. As mentioned above, possible first hits include genetic risk and maternal influenza or exposure to stress during the second trimester of pregnancy. Furthermore, minor physical anomalies may serve as a marker of a first hit. Unfortunately, first hits are difficult to prevent. One possible intervention to prevent some first hits may be to provide influenza vaccinations to women of childbearing age; but, unfortunately, similar interventions are not possible for other forms of first hits. Nevertheless, identifying persons who have experienced a first hit and reducing the likelihood of a second hit may prevent some cases of schizophrenia.

Identification of those who have experienced a first hit is an initial step. Intervention programs designed to ameliorate harmful situations in at-risk persons may serve as a second step in preventing cases of schizophrenia. If such children are separated from their parents, for example, extra special care might be taken to provide supportive care-takers. In addition, research suggests that institutionalization may be particularly harmful for high-risk children [26].¹¹ Providing selected foster homes as an alternative to institutions may be particularly valuable for these children.

Conclusions

Research suggests the importance of poor family relationships and parental loss in the development of schizophrenia. The association, however, appears relevant only for children already at risk for schizophrenia. The combination of a predisposition to schizophrenia (i.e., sustaining a “first hit”) and a disharmonious family or loss of a parent (i.e., a “second hit”) increases the risk for schizophrenia. The increased risk appears clinically relevant.

In light of this research, intervention strategies may be helpful at two different time points: early assessment procedures may reveal the occurrence of a first hit that can put a child at risk for schizophrenia; then, interventions targeting the attenuation of second hits for those identified as having experienced a first hit may prevent the development of schizophrenia in vulnerable children.

Notes

1. A. Talovic (1984) High risk for schizophrenia: Father’s contribution to child outcome. Ph.D. dissertation, University of Southern California.

2. J. Schiffman, J. LaBrie, S. Mednick, T. Cannon, J. Parnas, & F. Schulsinger. Perception of parent-child relationships in high-risk families, and adult schizophrenia outcome of offspring. Manuscript submitted for publication. University of Southern California.

3. J. Schiffman, J. LaBrie, S. Mednick, T. Cannon, J. Parnas, & F. Schulsinger. The two-hit model: A prospective investigation. Manuscript submitted for publication. University of Southern California.

4. J. Schiffman et al. Op. cit. (note 2).
5. J. Schiffman, C.E. Barr, S.A. Mednick, B.R. Mednick, M. Ekstrom, P. Munk-Jorgensen, & D. Gutkind. Very early parental separation: A risk factor for schizophrenia and other psychiatric disorders. Manuscript in preparation.
6. J. Schiffman et al. Op. cit. (note 3).
7. Ibid.
8. Ibid.
9. D.K. Kinney, W. Hyman, C. Greetham, & S. Tramer, S. (1999) Increased relative risk for schizophrenia and prenatal exposure to a severe tornado. Poster presentation at the VIIIth International Congress on Schizophrenia Research: A Biennial Convocation. Sante Fe, New Mexico.
10. J. Schiffman et al. Op. cit. (note 3).
11. D. Gutkind, B. Mednick, T. Cannon, J. Parnas, F. Schulsinger, & S.A. Mednick. Parental absence and schizophrenia—A 27-year follow-up of the Copenhagen High-Risk Cohort. Manuscript submitted for publication. University of Southern California.

References

1. Lukoff, D., Snyder, K., Ventura, J., & Neuchterlein, K.H. (1984) Life events, familial stress, and coping in the developmental course of schizophrenia. *Schizophrenia Bulletin*, 10, 258.
2. Byrne, C.P., Velamoor, V.R., Cernovsky, Z.Z., Cortese, L., & Loszтын, S. (1990) A comparison of borderline and schizophrenic patients for childhood life events and parent-child relationships. *Canadian Journal of Psychiatry*, 35, 590.
3. Roff, J.D., & Knight, R. (1981) Family characteristics, childhood symptoms, and adult outcome in schizophrenia. *Journal of Abnormal Psychology*, 90, 510.
4. Goldstein, M. (1987) The UCLA High-Risk Project. *Schizophrenia Bulletin*, 13, 505.
5. Granville-Grossman, K. (1966) Early bereavement and schizophrenia. *British Journal of Psychiatry*, 112, 1027.
6. Gregory, I. (1958) Studies of parental deprivation in psychiatric patients. *American Journal of Psychiatry*, 115, 432.
7. Wahl, C.W. (1956) Some antecedent factors in the family histories of 568 male schizophrenics of the United States Navy. *American Journal of Psychiatry*, 113, 201.
8. Ragan, P.V., & McGlashan, T.H. (1986) Childhood parental death and adult psychopathology. *American Journal of Psychiatry*, 143, 153.
9. Hilgard, J., & Newman, M. (1963) Parental loss by death in childhood as an aetiological factor among schizophrenic and alcoholic patients compared with a nonpatient community sample. *Journal of Nervous and Mental Disorders*, 137, 14.
10. Gay, M., & Tonge, W. (1967) The late effects of loss of parents in childhood. *British Journal of Psychiatry*, 113, 753.
11. Munro, A., & Griffiths, A. (1969) Some psychiatric nonsequelae of childhood bereavement. *British Journal of Psychiatry*, 115, 305.
12. Brill, N., & Liston, E. (1966) Parental loss in adults with emotional disorders. *Archives of General Psychiatry*, 14, 307.
13. Furukawa, T., Mizukawa, R., Hirai, T., Fujihara, S., Kitamura, T., & Takahashi, K. (1998) Childhood parental loss and schizophrenia: Evidence against pathogenic but for some pathoplastic effects. *Psychiatry Research*, 81, 353.

14. Maekikyroe, T., Sauvola, A., Moring, J., Vejjola, J., Nieminen, P., Jaervelin, M., & Isohanni, M. (1998) Hospital-treated psychiatric disorders in adults with a single-parent and two-parent family background: A 28-year follow-up of the 1966 Northern Finland Birth Cohort. *Family-Process*, 37, 335.
15. Watt, N.F., & Nicholi, A. (1979) Early death of a parent as an etiological factor in schizophrenia. *American Journal of Orthopsychiatry*, 49, 465.
16. Gottesman, I. (1984) Nature versus nurture in schizophrenia: The struggle continues. Commentary. *Integrative Psychiatry*, 2(4), 146.
17. Asarnow, J.R. (1988) Children at risk for schizophrenia: Converging lines of evidence. *Schizophrenia Bulletin*, 14, 613.
18. Mednick, S.A., & Schulsinger, F. (1965) A longitudinal study of children with a high risk for schizophrenia: A preliminary report. In S. Vandenberg (Ed.), *Methods and goals in human behavior genetics*. New York: Academic Press.
19. Burman, B., Mednick, S.A., Machón, R.A., Parnas, J., & Schulsinger, F. (1987) Children at high risk for schizophrenia: Parent and offspring perceptions of family relationships. *Journal of Abnormal Psychology*, 96, 364.
20. Mednick, S.A., Mura, E., Schulsinger, F., & Mednick, B. (1971) Perinatal conditions and infant development in children with schizophrenic parents. *Social Biology*, 18, Suppl. 2, p. 103.
21. Zachau-Chistiansen, B., & Ross, E.M. (1975) *Babies: Human development during the first year*. New York: Wiley.
22. Marcus, J., Hans, S., Nagler, S., Auerbach, J., Mirsky, A., & Aubrey, A. (1987) Review of the NIH Israeli Kibbutz—City Study and Jerusalem Infant Development study. *Schizophrenia Bulletin*, 13, 425.
23. Tienari, P. (1991) Interactions between genetic vulnerability and family environment. *Acta Psychiatrica Scandinavica*, 84, 460.
24. Parnas, J., Teasdale, T., & Schulsinger, H. (1985) Institutional rearing and diagnostic outcome in children of schizophrenic mothers. *Archives of General Psychiatry*, 42, 762.
25. Walker, E.F., Cudek, R., Mednick, S.A., & Schulsinger, F. (1981) The effects of parental absence and institutionalization on the development of clinical symptoms in high-risk children. *Acta Psychiatrica Scandinavica*, 63, 95.
26. Mednick, S.A., Watson, J.B., Huttunen, M., Cannon, T.D., Katila, H., Machón, R., Mednick, B., Hollister, M., Parnas, J., Schulsinger, F., Sajaniemi, N., Voldsgaard, P., Pyhala, R., Gutkind, D., & Wang, X. (1998) A two-hit working model of the etiology of schizophrenia. In M. Lenzenweger & R.H. Dworkin (Eds.), *Origins and development of schizophrenia: Advances in experimental psychopathology*. Washington, DC: American Psychological Association. Pp. 27–66.
27. Walker, E.F., & Diforio, D. (1997) Schizophrenia: A neural diathesis-stress model. *Psychological Review*, 104, 667.
28. Mednick, S.A., Machón, R.A., Huttunen, M.O., & Bonett, D. (1988) Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry*, 45, 189.
29. O'Callaghan, E., Sham, P., Takei, N., Glover, G., & Murray, R. (1991) Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet*, 337, 1248.
30. Kendell, R., & Kemp, I. (1989) Maternal influenza in the etiology of schizophrenia. *Archives of General Psychiatry*, 46, 878.

31. Mednick, S.A., Machón, R.A., Huttunen, M., & Barr, C. (1990) Influenza infection during gestation and adult schizophrenia: Response to Kendell and Kemp. *Archives of General Psychiatry*, 47, 875.
32. Green, M.F. (1998) *Schizophrenia from a neurocognitive perspective: Probing the impenetrable darkness*. Boston: Allyn and Bacon.
33. Guy, J.D., Majorski, L.V., Wallace, C.J., & Guy, M.P. (1983) The incidence of minor physical anomalies in adult male schizophrenics. *Schizophrenia Bulletin*, 9, 571.
34. Smith, D.W. (1976) *Recognizable patterns of human malformation: Genetic, embryologic and clinical aspects*. Philadelphia: W.B. Saunders.