Background: Premorbid neurocognitive, neuromotor, and behavioral function tends to be disturbed in schizophrenia. We previously demonstrated that a birth cohort clinically and serologically documented with prenatal rubella evidenced a marked increase in risk of nonaffective psychosis. In our study, we examined whether rubella-exposed subjects destined to develop schizophrenia and other schizophrenia spectrum disorders (SSD), compared with exposed control subjects, had greater impairment in several premorbid functions.

Methods: Subjects were interviewed using a direct, comprehensive research assessment and diagnosed by consensus. We compared the degree of IQ decline, as well as premorbid neuromotor and behavioral dysfunction, between rubella-exposed subjects who developed schizophrenia spectrum psychosis (SSP) and exposed control subjects from the cohort. We also compared the gestational timing of rubella infection between the cases and control subjects.

Results: This rubella-exposed birth cohort evidenced a markedly increased risk of SSD (20.4% or 11/53). Rubella-exposed SSP cases, compared with rubella-exposed control subjects, demonstrated a decline in IQ from childhood to adolescence, and increased premorbid neuromotor and behavioral abnormalities. Moreover, it appears that early gestational rubella infection may represent a period of increased vulnerability for SSD.

Conclusions: These findings link a known prenatal exposure, a deviant neurodevelopmental trajectory in childhood and adolescence, and SSP in adulthood within the same individuals.

Key Words: prenatal, rubella, German measles, premorbid, schizophrenia, neurodevelopmental

Introduction

After more than 100 years of research on schizophrenia, its origins have remained elusive. One of the most intractable barriers toward unraveling the etiologies of this devastating disorder has been the lack of a clear model of etiopathogenesis. Within the past 10 years, however, a compelling hypothesis with the potential to revolutionize our theoretical approach to this illness has gained considerable favor. Termed the neurodevelopmental hypothesis of schizophrenia, it posits that a disruption in development of the brain creates a vulnerability to the emergence of the disorder later in life (Waddington et al 1999).

One implication of the neurodevelopmental hypothesis is that prenatal environmental exposures, including viral infections, that disturb development of the fetal brain might be important risk factors for schizophrenia (Brown and Susser 1996; Susser et al 1999). In this article, we employ a novel strategy to examine whether prenatal exposure to a viral infection, the rubella virus, and associated premorbid functional abnormalities are related to the risk of adult schizophrenia and other schizophrenia spectrum disorders (SSD). Important strengths of this strategy include clinical and serologic documentation of in utero rubella exposure, longitudinal follow-up data on neurocognitive and other premorbid functions, and well-diagnosed cases of schizophrenia and other SSD.

The Neurodevelopmental Hypothesis of Schizophrenia

Evidence from several diverse areas of research has converged to support the neurodevelopmental hypothesis of schizophrenia. One of the strongest pieces of evidence in support of this hypothesis derives from studies that examined childhood neurocognition, neuromotor function, and behavior in individuals destined to develop schizophrenia. With regard to premorbid neurocognitive function, Jones et al (1994) demonstrated lower IQ, diminished educational test scores, and increased speech problems during childhood and adolescence among subjects who later developed schizophrenia. David et al (1997) showed that lower IQ scores at the time of military conscription...

With respect to neuromotor function, Walker et al (1994) found an increase in several neuromotor anomalies during childhood, including abnormal hand posture, choreathetoid movements, hypertonicity, and hypotonicity in preschizophrenic subjects compared with control subjects. Jones et al (1994) found subtle delays in milestones of motor development among subjects who were later diagnosed with schizophrenia.

With regard to deviant behaviors, Done et al (1994) found greater social maladaptation, including anxiety, hostility, and social withdrawal, at ages 7 and 11 among individuals who later developed schizophrenia. Jones et al (1994) also found increased anxiety in preschizophrenic patients, as well as less social confidence during adolescence and a preference for solitary play during childhood.

Other pieces of evidence provide further support for the neurodevelopmental hypothesis of schizophrenia. Patients with schizophrenia appear to have an increase in the number and severity of minor physical anomalies, subtle malformations reflective of embryonic disturbances in early gestation (Green et al 1989; Waddington 1993a, 1993b). Neuroimaging studies have documented several brain abnormalities, including ventriculomegaly and diminished volume of the hippocampus and other medial temporal lobe structures, among patients in their first episode of schizophrenia (Bogerts et al 1990; DeGreef et al 1992; Nopoulos et al 1995), suggesting that these anomalies were present before illness onset. Cavum septum pellucidum, a brain anomaly that likely reflects in utero disruption, also occurs at an increased rate among patients with schizophrenia (Nopoulos et al 1997).

Although the neurodevelopmental model of schizophrenia cannot explain all aspects of this illness, it does provide an important conceptual framework from which to generate testable hypotheses on potential causal factors. Schizophrenia certainly has a strong genetic basis, but there has been increasing suspicion that environmental risk factors may also play important etiopathogenic roles. The strongest evidence for this notion is that the discordance rate for schizophrenia among monozygotic co-twins is approximately 50% (McGuffin et al 1995). Because these twins are genetically identical, any phenotypic differences should reflect an environmental component. The affected members of these monozygotic twin pairs also have greater structural and functional brain anomalies (Suddath et al 1990; Berman et al 1992).

### Potential Role of Prenatal Viral Infection

Thus, environmental factors operating during the prenatal period have emerged as plausible risk factors for neurodevelopmental schizophrenia. Among the environmental agents examined, much attention has focused on prenatal viral infection, largely because viral insults are among the best known and most common causes of developmental brain disorders (Brown and Susser 1999). The vast majority of these studies have attempted to test whether prenatal exposure to influenza is associated with an increased risk of schizophrenia. In the most common type of research design, the risk of schizophrenia was compared between individuals who were in utero during known influenza epidemics and those who were unexposed. In the first of these studies, conducted in Finland, Mednick et al (1988) demonstrated that subjects who were in the second trimester of gestation during the 1957 influenza epidemic had a significantly increased risk of schizophrenia. Several subsequent studies modeled on that study replicated the second trimester association (Adams et al 1993; Kunugi et al 1995; McGrath et al 1994; O’Callaghan et al 1991), although other investigations have not replicated these findings (Erlenmeyer-Kimling et al 1994; Susser et al 1994; Torrey et al 1991). An additional research design utilizes data on maternal influenza infection in individuals; these studies did not show an association with schizophrenia in the offspring (Crow et al 1991; Cannon et al 1996).

These discrepant findings may be due to two limitations (Brown and Susser 1999). First, most studies defined the exposure using ecologic data (i.e., it was known that an individual was in utero at the time of an influenza epidemic but not whether influenza occurred during the pregnancy), rather than confirming the infection in individual pregnancies. In the studies that attempted to document influenza infection during pregnancy, cited above, exposure status was determined by midwife interviews of the mother after birth (Crow et al 1991; Cannon et al 1996), instead of clinically documenting maternal influenza at the time of its occurrence. This may have resulted in nondifferential misclassification of exposure status. Second, the diagnosis of schizophrenia in previous studies was ascertained from case registers or clinical records, rather than from research assessments. Although based on contemporary data, the lack of a standardized assessment may tend to result in diagnostic misclassification of the outcome. Nondifferential misclassification of exposure and outcome status may have acted to bias the findings toward the null in some studies.

A further critique of the influenza studies is that this virus was generally selected for study based on its relatively high frequency in the population, rather than on its biological plausibility as a risk factor for schizophrenia. Studies on the teratogenicity of prenatal exposure to
influenza are mixed; for instance, some have demonstrated associations with neural tube defects (Coffey and Jessop 1955; Hakosalo and Saxen 1971), whereas others have shown no such relation (Abramowitz 1958; Leck 1963). It is nonetheless conceivable that more subtle teratogenic effects of prenatal influenza, which may be potentially relevant to schizophrenia, have not been investigated. In addition, the putative increased risk of schizophrenia following maternal influenza could result from indirect mechanisms, rather than from direct infection of the fetal brain, as occurs in many teratogenic infections. For instance, an autoantibody response to maternal influenza has been postulated to occur in schizophrenia (Wright et al 1999).

Previous Study on Prenatal Rubella and Nonaffective Psychosis

One of the first infections to be documented as a cause of congenital central nervous system congenital anomalies is rubella. In 1941, Sir Norman Gregg reported a strong association between congenital cataracts and a rubella epidemic that shortly preceded these births (Gregg 1941). Over the subsequent years, the congenital rubella syndrome was broadened to include deafness, mental retardation, and many other developmental outcomes (South and Sever 1985). Dr. Stella Chess theorized that the consequences of this central nervous system (CNS) viral teratogen might also encompass psychiatric disorders (Chess et al 1971). To test this hypothesis, Chess and colleagues conducted psychiatric and psychologic assessments in the Rubella Birth Defects Evaluation Project (RBDEP), a cohort of children prenatally exposed to the 1964 rubella epidemic in New York City. The authors reported an increased risk of autism, separation anxiety disorder, and impaired social relations among these rubella-exposed children compared with population estimates (Chess et al 1971).

This cohort received further follow-up studies in adolescence and young adulthood, during which extensive psychiatric and psychological testing was performed. At the young adult follow-up, administered at age 21 to 23, the cohort received a structured psychiatric interview, the Diagnostic Interview Schedule for Children (DISC; Costello et al 1984), which permitted diagnoses of psychotic and other major psychiatric disorders in accord with DSM-III-R criteria. This provided a unique opportunity to test the prenatal viral hypothesis of schizophrenia. First, unlike other infections examined in relation to schizophrenia, all of the cohort members of the RBDEP were clinically documented as having been exposed in utero to rubella, and a large proportion of both mothers and offspring were serologically tested and confirmed as positive for the virus. Second, as discussed above, rubella is a plausable viral risk factor for schizophrenia because it is a known CNS teratogen. Third, in contrast to previous studies on prenatal viral infection and schizophrenia, we had access to diagnoses generated from a standardized, research-based psychiatric instrument.

We therefore assessed the frequency of psychiatric disorders in this rubella-exposed cohort (Brown et al 2000). Because the psychiatric assessment was considered to be a lay interview, our hypothesized diagnostic outcome was nonaffective psychosis because the correspondence between lay and clinical interview diagnoses was better for this broader outcome than for schizophrenia. For comparison, we assessed the risk of nonaffective psychosis in two age-matched, demographically comparable samples: a cohort in Albany and Saratoga counties in New York State (Cohen and Cohen 1996) and the Epidemiologic Catchment Area (ECA) sample (Robins and Regier 1991); both comparison samples received psychiatric assessments similar to that of the rubella-exposed cohort, except the interview was administered on computer for the rubella-exposed subjects and orally for the comparison samples. It can be safely assumed that the comparison samples were unexposed to rubella, which had a prevalence in pregnant women of approximately 0.1% during the time period of birth for the subjects in these samples.

In that study, we found a markedly and significantly increased risk of nonaffective psychosis in the rubella-exposed subjects, compared with both the Albany and Saratoga unexposed and the ECA unexposed (Brown et al 2000). The relative risks of nonaffective psychosis in the rubella-exposed subjects were greater than fivefold in comparison with the Albany and Saratoga unexposed subjects and greater than 16-fold in comparison with the ECA unexposed subjects. We showed that these results could not be accounted for by the high proportion of deafness in the rubella-exposed because the rates of nonaffective psychosis were similar between hearing-impaired and nonhearing-impaired individuals.

Study of Premorbid Function and Schizophrenia

The data obtained on this unique cohort provided us with a further opportunity: to elucidate the relation of premorbid dysfunction to later SSD. Although previous studies, reviewed above, yielded groundbreaking evidence of specific early antecedents of schizophrenia, they had two significant limitations. First, suspected early developmental factors that might explain these premorbid deficits, and the ensuing schizophrenic illness, could not be meaningfully delineated because of insufficient data on potential prenatal or childhood risk factors. Second, these investigators did not examine the relation between change in
premorbid neurocognitive function during childhood and adolescence and risk of adult schizophrenia. A prediction of two well-cited models of schizophrenia pathogenesis (Feinberg 1983; Weinberger 1987) is that adolescent individuals destined to develop schizophrenia should evidence a decline in neurocognitive performance before illness onset (see Discussion).

Fortunately, the RBDEP cohort permitted us to address both of these limitations. Extensive, longitudinal information on childhood and adolescent neurocognitive, neuromotor, and behavioral function was collected on virtually all rubella-exposed cohort members. To use these data to maximal advantage, however, we needed to obtain more precise diagnoses. In our previous study of nonaffective psychosis in the RBDEP cohort, the diagnostic assessments, although research-based, were conducted by lay interviewers and lacked sufficient symptom items to yield definitive diagnoses of SSD. Moreover, because the cohort members were aged only 21–23 years at the time of assessment, they had not passed through a large proportion of the risk period for the development of schizophrenia.

Hence, we conducted an additional follow-up of the rubella-exposed birth cohort 10 years after their initial assessment. This follow-up featured improved diagnostic precision from a more thorough and clinically based research diagnostic assessment, the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al 1994). In addition, the subjects, who are presently in mid-adulthood, have passed through more of the risk period for the development of SSD.

These unique design features thus provided the opportunity to further elucidate the relationship between pre-morbid function and risk of SSD in subjects with a known prenatal viral exposure. We hypothesized that rubella-exposed subjects who later developed SSD would evidence a decline in IQ from childhood to adolescence, as well as greater neuromotor and behavioral abnormalities, compared with rubella-exposed control subjects. The refined diagnoses and the available data on the gestational timing of rubella exposure also facilitated the examination of whether early gestational exposure to rubella posed a particularly increased risk of adult SSD, as it does for other manifestations of congenital rubella (South and Sever 1985).

Methods and Materials

Assessment of Risk of SSD in the RBDEP Cohort

DESCRIPTION OF BIRTH COHORT. The rubella-exposed birth cohort was derived from the RBDEP, which was established at New York University Medical Center in 1964, the year of a major rubella pandemic. The purpose of the RBDEP was to study the clinical manifestations of congenital rubella and develop appropriate management techniques (Chess et al 1971; Cooper et al 1969). The great majority of subjects were recruited by announcements and bulletins, which were disseminated to physicians throughout New York City, requesting referrals for pregnancies in which rubella was clinically diagnosed. A small minority of infants diagnosed with congenital rubella syndrome were also enrolled in the cohort. The total number of infants enrolled in the RBDEP was 243. Serologic confirmation of infection was obtained in the vast majority of mothers and infants tested.

The RBDEP cohort received follow-up assessments during childhood, adolescence, and young adulthood. Figure 1 depicts the numbers of subjects assessed at each follow-up. During each of these follow-ups, the investigators attempted to locate as many of the subjects in the original cohort as possible. At the young adult assessment, subjects meeting eligibility criteria were administered the DISC (Costello et al 1984). These criteria, which were established to enhance validity of the interview, included IQ ≥ 70 and no major physical handicaps (with the exception, in many cases, of deafness). We had previously demonstrated, in the RBDEP cohort, an increased risk of nonaffective psychosis in subjects meeting these criteria (see Introduction). In the second column of Figure 1, we present the numbers of subjects who met these eligibility criteria and who were followed up during adolescence, young adulthood, and our present study. Given that we also sought to administer a diagnostic interview in our study, we elected to target for follow-up the same subjects previously assessed with the DISC in young adulthood. As demonstrated in Figure 1, the subjects assessed for the present study constituted...
80% (53 of 66) of the eligible sample assessed in young adulthood.

TRACING AND LOCATION. Contact information, including addresses and telephone numbers of parents of cohort members, was abstracted from paper files of the adolescent follow-up of the RBDEP cohort. Because this information was at least 10 years old, we then instituted a series of increasingly comprehensive searches across electronic media (including national telephone directories CD, Edge, Autotrack Plus; Database Technologies Online, Boca Raton, FL), until a probable match emerged with the paper files or there was a sequential trail linking the individual to previous known addresses, telephone numbers, or to a social security number.

PARENT MAILING. Parents of cohort members were first sent a letter with information about the study, including a postcard on which they could provide contact information on the cohort members or indicate whether they preferred not to provide that information. For cohort members whose parents did not respond to the mailing, we obtained contact information from electronic searches (see “Tracing and Location”) and from organizations and schools for the deaf.

CONTACT OF COHORT MEMBERS. For cohort members who were located, a letter was mailed containing a postcard by which they could indicate their option to decline participation. Those subjects who did not decline participation were telephoned to provide information about the study, to answer questions, and to invite their participation. Subjects who agreed to participate were scheduled for the diagnostic assessment.

DIAGNOSTIC ASSESSMENTS. We used the DIGS as the diagnostic assessment. The DIGS is a polydiagnostic instrument that has been extensively tested for reliability with good results (Nurnberger et al 1994). This interview was administered by trained clinicians with a minimum of a master’s degree in a mental health field; all interviewers were blind to the study hypotheses. A certified sign language interpreter was present at all interviews for subjects who had a history of at least mild deafness. Subjects were diagnosed by consensus of two psychiatric diagnosticians in accord with DSM-IV criteria, following independent review of all DIGS material including the narrative.

For subjects who could not be located or who declined the interview, psychiatric diagnostic information was obtained using the Family Interview for Genetic Studies (FIGS; NIMH Molecular Genetics Initiative 1991), which was administered to cohort members’ mothers who agreed to participate. Subjects were diagnosed following review of the information by a psychiatric diagnostician.

Of the 66 subjects in the targeted sample, 48 received the DIGS, and an additional 3 subjects received the FIGS. Thus, we assessed 80.3% (53 of 66) of the targeted cohort members. Among the remaining 13 subjects, 3 were not interviewed because their parents did not permit us to contact them; 3 agreed to be interviewed but could not attend the interview because of logistical difficulties; 1 did not agree to be interviewed; 1 could not be located; and 5 could be located but not contacted, and their parents could not be reached for administration of the FIGS.

DEFINITION OF THE OUTCOME. Our primary outcome was defined as schizophrenia and other schizophrenia spectrum disorders (SSD), in accord with a previous definition (Kendler et al 1995; Kendler and Walsh 1995), based on evidence of familial aggregation of these disorders. This definition includes the following DSM-IV diagnoses: schizophrenia, schizoaffective disorder, psychotic disorder NOS, delusional disorder, schizotypal personality disorder, and paranoid personality disorder.

Premorbid Function as a Predictor of Adult Schizophrenia Spectrum Psychosis (SSP)

DEFINITION OF GROUPS FOR COMPARISON. In a case-control design nested within the rubella-exposed cohort described above (see Methods), we compared premorbid IQ, neuromotor dysfunction, and deviant behaviors between subjects diagnosed with SSP and control subjects. Cases with schizophrenia spectrum personality disorders were excluded from the main analysis because these disorders by definition do not have a clear age of onset, which is required to identify a function as “premorbid.” The control subjects were rubella-exposed individuals from this birth cohort who were free of both SSD and major affective disorders. Subjects with major affective disorders were excluded as control subjects because SSD and affective disorders may share certain developmental precursors (van Os et al 1997). As demonstrated in Table 1, the case and control groups were generally similar with respect to age, ethnicity, and socioeconomic status, although the proportion of male subjects was somewhat higher in the SSD group (this is discussed further in Results). The SSD cases and control subjects were also compared with regard to hearing ability, which was found to be similar between the two groups.

CHILDHOOD AND ADOLESCENT FOLLOW-UP ASSESSMENTS. During childhood (mean age 8) and adolescence (mean age 13), members of the RBDEP birth cohort were
administered intellectual, behavioral, psychosocial, and psychiatric assessments. A virtually complete data set containing the results of these assessments was available for these two follow-ups. Using these data, we compared the occurrence of premorbid abnormalities demonstrated in previous studies to be predictive of SSD between rubella-exposed SSD cases and control subjects. Based on these previous studies, we selected the following domains of premorbid function: IQ, neuromotor dysfunction and mannerisms, and several deviant behaviors.

**ASSESSMENT INSTRUMENTS.** We assessed IQ with the Wechsler Intelligence Scale for Children (WISC) during childhood and the Wechsler Intelligence Scale for Children-Revised (WISC–R) during adolescence. For those subjects with deafness, a certified sign interpreter assisted. Although the verbal IQ scale was administered to the deaf children wherever feasible, it was considered too unreliable in this predominantly deaf sample. Therefore, the performance IQ scale and its subtests (picture completion, picture arrangement, block design, and object assembly) were used to determine cognitive function. As noted above, all subjects who were targeted for the psychiatric interview in mid-adulthood had IQ > 70.

Neuromotor status was assessed using a clinical exam administered by a neurologist. Subjects were rated in accord with the criteria of Chess and Hassibi (1978). These criteria were operationalized on a 5-point scale, as follows: 1 (profound dysfunction), 2 (severe dysfunction), 3 (moderate dysfunction), 4 (mild dysfunction), and 5 (normal). Further details on the definitions for each of these ratings are provided in Chess and Hassibi (1978). Data on neuromotor status were available for only the adolescent follow-up. For our study, “neuromotor abnormality” was defined as a rating of at least mild neuromotor dysfunction (i.e., a rating < 5).

Mannerisms were coded by trained raters using a global score. All ratings were done by consensus of two raters. The scale was defined as 1 (extremely prominent), 2 (severe), 3 (moderate), 4 (mild), and 5 (insignificant or none). For the present study, “mannerisms” were considered to be present if there was a rating of at least mild mannerisms (i.e., a rating < 5). Data were available from both the childhood and adolescent follow-ups.

A semistructured interview regarding a battery of deviant childhood behaviors was administered to the parents and teachers of each subject. The results of these interviews were reviewed by trained chart abstractors, and the presence or absence of deviant behaviors were coded based on operationalized criteria. For our study, we focused on five deviant behaviors suggested in previous studies, reviewed above, to be disturbed in children destined to develop schizophrenia or that represent prominent clinical features of patients with schizophrenia (Wing 1995). These were aggressiveness, temper tantrums, short attention span and distractibility, emotional immaturity, and suspiciousness. Data were available from both the childhood and adolescent follow-up assessment, and from interviews of the parent and the teacher for both childhood and adolescence.

**Data Analysis**

We first examined the frequency distributions and parameters of the variables. We then examined whether several relevant demographic variables differed between SSP cases and control subjects. Because the groups did not differ on these variables, they were not controlled for in subsequent analyses. To compare the groups on performance IQ at each time point, a repeated measures analysis of variance (ANOVA) was conducted to test for between group effects (case vs. control subject), time effects (childhood vs. adolescence), and their interaction. To further address this question, we used Fisher’s Exact Test to compare the groups with respect to the proportions evidencing a decline in performance IQ between childhood and adolescence. Because of the relative rarity of neuromotor dysfunction, mannerisms, and deviant behaviors and because of the modest number of subjects, these categories were collapsed for the statistical analysis. The SSP cases and control subjects were compared with respect to the presence of any of these premorbid abnormalities using Fisher’s Exact Test. We also used Fisher’s Exact Test to compare the gestational timing of prenatal rubella between cases and control subjects.

**Results**

**Risk of Schizophrenia Spectrum Disorders**

The numbers and proportions of interviewed subjects with each DSM-IV diagnosis in the rubella-exposed cohort are presented in Table 2. We found that 20.4% (11 of 53) of the sample was diagnosed with SSD. For the 48 subjects diagnosed after receiving the DIGS, 20.8% (10) received a SSD diagnosis. Although we did not assess psychiatric disorders in a cohort unexposed to rubella, this figure is substantially higher than population estimates from previ-

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia Spectrum Disorders</td>
<td>11</td>
<td>20.8</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>3</td>
<td>5.7</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>Schizotypal personality disorder</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Paranoid personality disorder</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Affective Disorders</td>
<td>14</td>
<td>26.4</td>
</tr>
<tr>
<td>Bipolar affective disorder</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major depressive disorder, unipolar</td>
<td>13</td>
<td>24.5</td>
</tr>
<tr>
<td>Mood disorder NOS</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social phobia</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Alcohol/Substance Abuse/Dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis dependence</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Childhood Disorders</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Disorder of infancy/childhood/adolescence NOS</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Uncomplicated bereavement</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Learning disorder</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>No Psychiatric Diagnosis</td>
<td>22</td>
<td>41.5</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic Breakdown (DSM-IV) of Rubella-Exposed Subjects in the RBDEP Cohort (Primary Axis I Diagnoses Only), N = 53
Rubella, Premorbid Anomalies, and Schizophrenia

Premorbid Abnormalities in Relation to Adult SSD

**Premorbid Performance IQ.** The mean (SD) performance IQ scores for the SSP group and the control group during childhood and adolescence, respectively, are presented in Table 3. As demonstrated, the mean childhood IQ in the SSP cases is less than in control subjects, but this difference widens substantially during adolescence. This is due to an approximately 11-point decline in IQ from childhood to adolescence in the SSP cases, compared with a less than 3-point decline in the control subjects. Repeated measures ANOVA revealed a significant group (SSP cases vs. control subjects) by time (childhood vs. adolescence) interaction \( (F = 5.46, p = .03) \), indicating that the slopes generated by the respective changes in IQ from childhood to adolescence differed significantly between the SSP group and the control group; this difference was accounted for by a greater IQ decline in the SSP group.

To examine whether the decline in mean IQ in the SSP cases was accounted for by a small number of outliers, we compared the respective proportions of subjects with an IQ decline between the SSP group and the control group (Table 4). This was not the case: the proportion of SSP cases demonstrating an IQ decline of at least 3 points between the childhood and adolescent assessments was 87.5%, compared with 33% in the control group \( (p = .02, \text{ Fisher’s Exact Test}) \).

In an additional analysis, we examined whether the findings persisted when all cases of SSD (i.e., the inclusion of schizophrenia spectrum personality disorders) were examined for IQ decline. We found that 73% (8 of 11) of subjects with SSD had an IQ decline from childhood to adolescence, compared with 37% (10 of 27) of control subjects (Fisher \( p = .046 \)).

Finally, given that the proportion of male subjects in the SSD group was somewhat higher than the proportion of female subjects, we evaluated the possibility that the finding on IQ decline was confounded by gender by comparing the proportions of subjects with IQ decline between male and female subjects in the assessed sample. The respective proportions of subjects with an IQ decline were 65% (15/23) for male subjects and 61% (17/28) for female subjects, arguing against the possibility of confounding by gender.

**Other Premorbid Abnormalities**

The proportions of subjects with neuromotor dysfunction, mannerisms, and deviant behaviors in the SSP group and the control groups are presented in Table 5. As demonstrated in the table, the SSP group, compared with the control group, had more subjects diagnosed with each of these premorbid abnormalities. Because of the relatively small numbers of subjects with these abnormalities, we

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Table 3. Premorbid Performance IQ* in Rubella-Exposed Subjects: Comparison between SSP Cases and Control Subjects Assessed during Childhood and Adolescence

<table>
<thead>
<tr>
<th></th>
<th>Childhood</th>
<th>Adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>SSP</td>
<td>87.5 (13.6)</td>
<td>89.5 (14.8)</td>
</tr>
<tr>
<td>Controls</td>
<td>60.7 (15.2)</td>
<td>64.3 (14.8)</td>
</tr>
</tbody>
</table>

SSP, schizophrenia spectrum psychosis.

Table 4. Proportions of Rubella-Exposed Subjects with Decline in IQa from Childhood to Adolescence: Comparison of SSP Cases and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>N with IQ decline</th>
<th>% with IQ decline</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSP</td>
<td>8</td>
<td>7</td>
<td>87.5</td>
<td>.02a</td>
</tr>
<tr>
<td>Control</td>
<td>28c</td>
<td>10</td>
<td>37.0</td>
<td></td>
</tr>
</tbody>
</table>

SSP, schizophrenia spectrum psychosis.

---

Table 5. Premorbid Neuromotor Dysfunction, Mannerisms, and Deviant Behaviors in Rubella-Exposed Subjects: Comparisons between SSP Cases (N = 8) and Control Subjects (N = 28)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromotor dysfunctiona</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSP</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Control subjects</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>Mannerismsb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSP</td>
<td>4</td>
<td>50.0</td>
</tr>
<tr>
<td>Control subjects</td>
<td>8</td>
<td>28.6</td>
</tr>
<tr>
<td>Deviant behaviorsc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSP</td>
<td>8</td>
<td>100.0</td>
</tr>
<tr>
<td>Control subjects</td>
<td>17</td>
<td>60.7</td>
</tr>
</tbody>
</table>

SSP, schizophrenia spectrum psychosis.

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References

1. Eaton 1985; Kendler et al 1996. The age of onset of SSD was at least 18 in all cases; thus, the last of the premorbid assessments was conducted at least 5 years before the onset of psychosis.
the small sample sizes. Jones et al 1994; Walker et al 1994). In those studies, the way (David et al 1997; Erlenmeyer-Kimling et al 1991; premorbid abnormalities in schizophrenia in an important signs of SSP could explain the findings. before the onset of psychosis, it is unlikely that prodromal premorbid assessments was conducted at least 5 years within the same individuals. Because the last of the malities predictive of later SSP and to the SSP outcome linking a specific prenatal exposure to premorbid abnor-
viral exposure. These results provide the first evidence predicting adult SSP in a birth cohort with a known prenatal exposure. With regard to potential causal mechanisms by which rubella may lead to schizophrenia, gross neuro-
pathologic abnormalities in congenital rubella syndrome provide some important clues. In a magnetic resonance imaging (MRI) study, Lim et al (1995) demonstrated that congenital rubella patients with schizophrenia-like symp-
toms had ventriculomegaly, significantly diminished cor-
tical gray matter volume, and a similar pattern of gray matter volume deficit; all of these abnormalities were also found in a comparison group of unexposed patients with schizophrenia. These findings suggest a concordance with respect to several relevant aspects of brain pathology between congenital rubella and schizophrenia, which may be relevant to some or all of the premorbid deficits observed.

**Discussion**

We have demonstrated that premorbid abnormalities, including IQ decline between childhood and adolescence, predict adult SSP in a birth cohort with a known prenatal viral exposure. These results provide the first evidence linking a specific prenatal exposure to premorbid abnormalities predictive of later SSP and to the SSP outcome within the same individuals. Because the last of the premorbid assessments was conducted at least 5 years before the onset of psychosis, it is unlikely that prodromal signs of SSP could explain the findings.

These data extend the results of previous studies on premorbid abnormalities in schizophrenia in an important way (David et al 1997; Erlenmeyer-Kimling et al 1991; Jones et al 1994; Walker et al 1994). In those studies, the etiology of the premorbid abnormalities was not known, and premorbid IQ and other neurocognitive functions at more than one point in time were not available on sufficient numbers of cases to permit a meaningful analysis. In contrast, the precise documentation of exposure, and complete data on premorbid function in our cohort, provides evidence that a prenatally induced brain lesion can play a role in such premorbid abnormalities. Moreover, a decline in premorbid intellect from childhood to adolescence, revealed by the longitudinal data on IQ, suggests a dynamic pathogenic process that antedates the illness and that ultimately becomes expressed in adulthood as SSP. Although the findings on premorbid neuromotor and behavioral abnormalities fell short of statistical signif-
ificance, they appear to warrant further study.

**BIOLOGICAL PLAUSIBILITY AND CAUSAL MECHA-
NISMS.** The biological plausibility of prenatal rubella as a risk factor for schizophrenia is substantive (see Brown and Susser 1999 for review). Rubella virus in pregnancy leads to placental infection, resulting in fetal invasion (Whitley and Stagno 1991). The virus has numerous teratogenic effects, many of which involve disruption in development of the CNS. Neurodevelopmental disorders strongly associated with rubella include sensorineural deafness, mental retardation, learning disabilities, and cerebral palsy (South and Sever 1985). Each of these disorders, or their associated manifestations, have been reported to occur, to varying degrees, in schizophrenia (David et al 1995; Griffith et al 1994; Reid 1989; Walker et al 1994). With regard to potential causal mechanisms by which rubella may lead to schizophrenia, gross neuro-
pathologic abnormalities in congenital rubella syndrome provide some important clues. In a magnetic resonance imaging (MRI) study, Lim et al (1995) demonstrated that congenital rubella patients with schizophrenia-like symp-
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Neuropathologic findings gleaned from ultrastructural investigations suggest several different mechanisms by which rubella may induce developmental damage. First, rubella acts to inhibit mitosis, resulting in hypocellularity and diminished brain growth, leading in turn to microcephaly in some cases (Boue and Boue 1969; Rorke 1973; South and Sever 1985). This process also causes retardation of myelination because of reduced replication of oligodendrocytes (Kemper et al 1973). Some neuropatho-

### Table 6. Gestational Timing of Maternal Rubella Infection: Comparison of SSD Cases and Control Subjects

<table>
<thead>
<tr>
<th>Gestational month</th>
<th>SSD (N = 9)</th>
<th>Control Subjects (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>44.4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>33.3</td>
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<td>5</td>
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<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>&gt;6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SSP, schizophrenic spectrum psychosis.

aData available on 9 of 11 SSD cases.

bData available on 22 of 28 control subjects.
logic studies of schizophrenia have revealed abnormalities in the anterior cingulate, frontopolar cortex, entorhinal cortex, and hippocampus that may be viewed as consistent with neuronal loss (Beasley and Reynolds 1997; Benes et al 1991; Falkai and Bogerts 1986). There have, however, been several notable nonreplications of these findings, and there is mounting evidence that in some brain regions, neuronal density is actually increased in schizophrenia (Selemon and Goldman-Rakic 1999).

In a second putative mechanism, gestational rubella induces a proinflammatory immune response, leading to cerebrovascular damage in the fetal circulation, including endothelial destruction and pericapillary collections of granular material (Rorke et al 1968; Townsend 1994). This process results in ischemic damage, with the necrotic foci following the damaged blood vessels or their terminal supply fields. Rubella also induces an autoimmune response against several endocrine organs (Clarke et al 1984) and thus conceivably could damage the brain through such a mechanism.

The pathogenic mechanisms may not necessarily be specific to prenatal rubella but could extend to other viruses as well. Maternal fever, or other consequences of maternal viral infection, may also mediate the observed association.

**GESTATIONAL TIMING.** As presented above, the 1st and 2nd gestational months may represent a period of especially increased vulnerability to the development of SSD. This suggests that a rubella-induced disturbance in embryogenesis may be relevant to the pathogenesis of SSD, consistent with the well-documented increased vulnerability to the anomalies comprising congenital rubella syndrome following early gestational exposure (South and Sever 1985). This developmental period consists of the early embryonic stages, including cleavage and implantation; formation of the major divisions of the brain and subsequently the early cerebral hemispheres; creation and closure of the neural tube; extensive development of the hippocampus, amygdaloïd, hypothalamic, and thalamic regions, and formation of the cortical plate (O'Rahilly and Muller 1999). Given the relatively undifferentiated nature of the brain during this developmental period and the diversity of regional brain abnormalities implicated in schizophrenia, it is difficult to attribute the pathogenesis of schizophrenia following prenatal rubella to any particular developmental stage or brain area. It should also be noted that a disruption in embryogenesis may have downstream effects on later developmental stages. Moreover, active rubella infection has been shown to persist in the infant as late as 18 months following birth (South and Sever 1985), suggesting that viral effects on brain development during the postnatal period may also play important contributory roles.

**Models of Pathogenesis**

Two prominent models of pathogenesis of schizophrenia, mentioned briefly in the Introduction, appear most relevant to our findings and thereby provide us with a point of departure toward delineating the relationships observed between prenatal rubella, premorbid dysfunction, and adult schizophrenia. Reciprocally, our findings may have implications for validating and further elaborating these models.

The first model, exemplified by Weinberger’s hypothesis (Weinberger 1987), argues that a fixed early brain lesion interacts with later maturational events during adolescence to produce the psychopathology of schizophrenia in early adulthood. One of the most compelling pieces of evidence cited in this model is that the dorsolateral prefrontal cortex (DLPFC), a brain region that is underactivated in schizophrenic patients challenged with working memory tasks (Weinberger et al 1986), reaches functional maturity during late adolescence and early adulthood. This evidence includes studies in monkeys indicating that a DLPFC lesion has no marked effect on delayed-response tasks (a measure of DLPFC function) during infancy or the prepubescent period but has severe consequences for the performance of these tasks during adulthood (Goldman and Alexander 1977). Weinberger (1987) discussed further evidence from previous studies that dopamine, the neurotransmitter most clearly implicated in the pathophysiology of schizophrenia, plays a key role in functions subserved by the DLPFC. With regard to brain development, postnatal changes occur in dopamine tissue concentrations and synthesis rates in the prefrontal cortex of rhesus monkeys, with peak values demonstrated at the onset of puberty (Goldman-Rakic and Brown 1982). Rosenberg and Lewis (1995) demonstrated in rhesus monkeys a marked increase in the density of tyrosine hydroxylase-positive varicosities (predominantly reflecting dopamine axons) in the middle cortical layers, which reached a peak at the onset of puberty.

An alternative model of schizophrenia pathogenesis was exemplified by Feinberg’s hypothesis (Feinberg 1983). In contrast to Weinberger, Feinberg posited a pathogenic maturational process during adolescence that leads to schizophrenia through a defect in reorganization of brain function. According to Feinberg, these changes could be accounted for in large part by the rather striking decline in synaptic density, termed programmed synaptic elimination, shown to occur in humans between late childhood and early adolescence (Huttenlocher 1979). In this model, schizophrenia could result from a fault in programmed synaptic elimination during adolescence, such that “too many, too few, or the wrong synapses” are eliminated. In support of this model, Feinberg (1983) cited evidence from psychophysiology studies demonstrating profound
changes during adolescence in the sleep electroencephalogram; alterations in event-related potentials, such as the P300 wave; and a decline in cortical metabolic rate.

The recent literature has provided further evidence in support of this model. Findings in schizophrenia are consistent with an exaggerated loss of synapses in this disorder. Evidence of increased neuronal density in the prefrontal cortex (Selemon et al. 1995; Selemon and Goldman-Rakic 1999) suggests a reduction in interneuronal neuropil, which is largely comprised of synapses. Although consistent with a loss of synapses, they do not, however, specify the period of life during which this alteration occurs. Neuroimaging studies that have followed childhood-onset schizophrenia cases during adolescence have demonstrated an exaggerated and progressive decline in volume of cortical gray matter (Rapoport et al. 1999), cerebrum and hippocampus, and progressive enlargement of the lateral ventricles (Giedd et al. 1999). These authors noted that the results might be accounted for by excessive synaptic pruning in the cases. This finding is of particular relevance to our study, given that childhood-onset cases represent a developmental subtype of schizophrenia. Decreases in the ratio of gray to white matter during normal childhood and adolescence (Thompson et al. 1985) and peripubertal reduction in volume of cortical gray matter (Jernigan and Tallal 1990) also have been demonstrated, consistent with large-scale synaptic elimination during this developmental period. Interestingly, in a study cited above (Lim et al. 1995), patients with congenital rubella and schizophrenia had decreased volume of cortical gray matter, but not white matter. Keshavan et al. (1994) also reported several findings in schizophrenia that are consistent with a loss of synapses in later development.

**Delineation of Pathogenic Mechanisms**

These models provide a heuristic framework with which to delineate pathogenic mechanisms in early and later development that may underlie our findings. Although speculative, we wish to suggest two potential interpretations. The first derives from a model exemplified by Weinberger’s hypothesis (Weinberger 1987). Our subjects experienced an early brain insult, in this case, from prenatal exposure to rubella, which manifested as a mildly decreased IQ in childhood and as neuromotor and behavioral abnormalities in childhood and adolescence. In accord with the model, one could argue that between childhood and adolescence, the deterioration in IQ among certain individuals was due to an interaction between this early brain lesion and functional maturation of brain regions subserving more complex mental functions. Arnsten and Goldman-Rakic (1985) suggested that the maturation of dopamine systems in the prefrontal cortex during adolescence (discussed under Models of Pathogenesis above) may explain certain cognitive abilities that emerge during that developmental period. It is therefore conceivable that a disturbance in this developmental process may have contributed to the IQ decline observed in our study and also may have created a vulnerability to adult SSD. It is worth noting that our findings underscore an implication of this model that is not explicitly stated: as mesocortical dopamine afferents mature during puberty, one might expect to observe the emergence of subtle neurocognitive deterioration at that time in those with the putative early brain “lesion” and the tendency to develop adult schizophrenia. This model focuses instead on the onset of diagnosable schizophrenia, which more typically emerges from a few to as many as 10 to 15 years after the end of adolescence.

The application of aspects of a model exemplified by Feinberg (1983) to our data provides a second, and perhaps equally compelling, interpretation. Although this model does not include a prenatal insult, it could nonetheless be argued that, in susceptible individuals, a brain lesion induced by prenatal rubella could initiate a cascade of events that reverberate throughout development. This pathogenic process could disrupt programmed synaptic elimination, resulting in neurocognitive deterioration between childhood and adolescence and contributing to increased vulnerability to schizophrenia in adulthood. This explanation is of particular interest, given that much of the decline of synaptic density found by Huttenlocher (1979) occurred between the ages at which our subjects were assessed during childhood and adolescence. This process might also explain the decrement in IQ between these two time periods in our study, because, as argued by Feinberg (1983), the elimination of redundant synapses may be responsible in part for more efficient utilization of neuronal networks. This ability may give rise to the complex problem solving and abstract thought that characteristically emerges during adolescence. Indeed, subjects with particular types of mental retardation appear to have either unusually high or low synaptic densities (Cragg 1975; Ferrer and Gullotta 1990; Huttenlocher 1979).

**Limitations**

Limitations of the studies presented herein include the following.

1. **Lack of an unexposed cohort.** The absence of a birth cohort unexposed to rubella, and representative of the exposed cohort, does not permit us to accurately estimate the effect size. Nonetheless, we can approximate this figure by comparing the risk of SSP in the rubella cohort with population estimates of the risk of nonaffective psychosis, which are between
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0.5% and 1% (Kendler et al 1996). Therefore, given the greater-than-15% prevalence of SSP in the rubella-exposed birth cohort, this would suggest a relative risk of approximately 15-fold.

2. Psychotic disorder NOS. As noted in Table 1, 4 of the 11 subjects with SSD were diagnosed with psychotic disorder NOS. It could therefore be argued that our findings could be explained to some degree by the presence of atypical psychotic disorders that bear little phenomenologic resemblance to schizophrenia. Each of our cases of psychotic disorder NOS, however, had clear evidence of psychotic symptoms frequently found in schizophrenia, including auditory hallucinations, persecutory delusions, and mind reading; for 3 of the 4 cases, these symptoms were chronic.

3. Deafness. It could be argued that deafness may have played a role in the development of SSD. Our findings, however, argue otherwise. As demonstrated in Table 1, hearing ability (measured on a continuous scale) was similar between the SSD cases and the control subjects, and the proportion of subjects with normal hearing or slight hearing loss was the same in the SSD cases (36% or 4/11), compared with the control subjects (32% or 9/28). Second, previous studies that examined the relationship between deafness and psychosis are inconclusive. Altshuler and Sarlin (1969) found a 2.5% prevalence of schizophrenia in hospitalized deaf subjects, although selection bias and differences in diagnostic standards between deaf and hearing patients may have contributed to a spurious association. Severe hearing impairment in military inductees was associated with an increased risk of schizophrenia (David et al 1995), but hearing dysfunction could have resulted from intrauterine infections such as rubella.

4. Potential for selection bias. We first consider whether selection bias may have resulted in a spuriously increased risk of SSD in our cohort. Our follow-up rate of more than 80% (53) of the 66 targeted subjects was well above acceptable standards for prospective cohort studies and thus is unlikely to lead to appreciable bias. Because these 66 targeted subjects were derived from an eligible sample of 131 assessed in adolescence, it could be argued, however, that selection bias may have led to a spuriously increased risk of SSD; however, a sensitivity analysis assuming that none of those lost to follow-up had SSD yielded a prevalence of 8.4% (11/131), which is still substantially elevated compared with population estimates. Moreover, the 53 eligible, assessed subjects and the 78 eligible, unassessed subjects were similar to one another on age (all subjects were age 33–34 during the time period of our study), gender (% male: assessed = 45% [n = 24], unassessed = 59% [n = 46]; Fisher’s p = .15), and ethnicity (% white: assessed = 75% [n = 40], unassessed: 80% [n = 62]; \( \chi^2 = 1.09, p = .58 \)), suggesting that the assessed subjects were representative of the sample from which they were derived. Furthermore, bias in selecting individuals with more severe manifestations of rubella was obviated by our criterion of excluding subjects with mental retardation and multiple physical handicaps. Second, we specifically consider whether selection bias may have given rise to a spurious increase in premorbid abnormalities in SSD cases compared with control subjects. This appears to be unlikely for two reasons. First, all of the SSD cases and control subjects in our study derived from a single birth cohort, and uniform selection procedures were used at each follow-up assessment. Second, to address the possibility that differential loss to follow-up may have produced a spurious association between IQ decline and SSP, we examined whether the proportions of subjects with IQ decline differed between the assessed and unassessed subjects, a necessary condition for this type of bias. These proportions were similar: 53% (27 of 51 assessed) versus 46% (32 of 70 unassessed) manifested at least a 3-point decline in IQ (\( \chi^2 = 0.62, p = .43 \)).

5. Lack of data on family history of psychiatric illness. It is worth noting that despite the high prevalence of SSD in the rubella-exposed subjects, the majority did not develop SSD. Although early gestational timing of the infection appears to play a role, one must also consider the potential effect of genetic predisposition to psychiatric disorders, especially SSD. To address this question, we shall attempt to obtain data on family history of psychiatric illness in future work.

6. Relatively small sample size. The number of rubella-exposed cases of SSP is relatively small. We believe, however, that the small sample size is counterbalanced by the high-quality, prospective data and the biological plausibility and coherence of the findings presented.

7. Lack of data on social environment and IQ decline. It is conceivable that a dynamic interaction between early signs of congenital rubella and the social environment could have played a role in the IQ decline observed in our cases. Although we found no evidence that indicators of the social environment, such as socioeconomic status, differed between subjects with clear manifestations of congen-
Rubella and those without such manifestations, our data were not sufficient to examine the interaction between these two factors.

Support for Causality

Although causality is usually difficult to prove, the data support the three essential properties of a causal relationship (Hill 1965). These are: 1) Association. A strong association between prenatal rubella and SSD—greater than 10-fold the risk in the unexposed population—provides strong evidence that the association is valid; 2) Temporal order. The study is designed such that there is no knowledge of the outcome when the exposure is assessed because the rubella exposure clearly precedes the SSD outcome by many years. 3) Direction (lack of confounding). Three lines of evidence support this property. First, as stated in 1 above, the association is strong. Second, the association persisted when potential confounders were controlled. Third, as reviewed above (see Introduction and Discussion), the relation between prenatal rubella and SSD is biologically plausible. Our study provides two further pieces of evidence that support causality: verification of the diagnosis of SSD and the demonstration of a relation between premorbid antecedents and risk of SSP.

Conclusions

In summary, we have provided further validation for a markedly increased risk of SSD in a birth cohort with prenatal exposure to rubella. Moreover, rubella-exposed subjects destined to develop SSD, compared with rubella-exposed control subjects, had evidence of a deviant neurodevelopmental trajectory, manifested by increased premorbid abnormalities characteristic of patients with schizophrenia and an IQ decline between childhood and adolescence. These findings provide further support for prenatal rubella as an etiology of SSD, as well as empirical support for pathogenic models of this disorder. Future studies are essential to independently replicate these findings in other cohorts, to examine structural and functional indicators of brain pathology among rubella-exposed SSD cases and control subjects, and to investigate potential interactions between prenatal rubella exposure and vulnerability genes.

Rubella has been virtually eliminated in industrialized countries; however, it remains a threat in many developing countries. Our findings therefore may have implications for prevention of SSD. Moreover, these findings may encourage further work on other prenatal viral agents in the etiopathogenesis of schizophrenia.

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