Childhood-Onset Schizophrenia: History of the Concept and Recent Studies

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Abstract

Schizophrenic disorders in childhood are rare: 0.1–1 percent of all schizophrenic disorders manifest themselves before age 10, and 4 percent before age 15. There is, however, a remarkable increase in schizophrenia during adolescence. Age and developmental stage also influence symptoms, course, and outcome. The evidence for a male preponderance in the very early-onset group (< 14) does not apply for adolescents over age 14. The presence of positive and negative precursor symptoms can be demonstrated in child and adolescent schizophrenia before the first clinical manifestation leading to inpatient treatment. With regard to pharmacologic treatment, atypical neuroleptics such as clozapine can be used successfully. As to outcome, schizophrenic psychoses with early manifestation have a poor prognosis. The patients' premorbid personality also seems to be of great importance: A poor prognosis can be found in patients who were cognitively impaired, shy, introverted, and withdrawn before the beginning of their psychotic state.

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Hermann Emminghaus (1887) wrote the first textbook on child psychiatry, *Psychic Disturbances of Childhood.* This text described childhood psychosis as "cerebral neurasthenia" and defined this disorder as "neurosis of the brain characterized by a reduction of cognitive (intellectual) abilities, mood changes, sleep disturbances and manifold anomalies of innervation with a subacute or chronic course and different states of outcome" (p. 134). He also believed that neuropathic children are predisposed to psychotic states and that the etiology of the disorders lies in disturbances of the blood vessels of the cortex.

Emminghaus was also the first (to our knowledge) to introduce a developmental perspective into child psychiatry, with special focus on psychoses. He writes, after complaining that there is no systematic and general symptomatology of childhood psychoses, that it is the task of psychopathology to study the anomalies of the mind through all developmental stages and to differentiate normal from pathologic psychic processes.

At the beginning of this century, Kraepelin (1913) distinguished two kinds of endogenous psychoses: dementia praecox and manic-depressive psychoses. Kraepelin went on to develop further differentiations, but his successors continued to use this simplistic dichotomy.

The term "schizophrenia" was introduced by Eugen Bleuler (1911) who spoke of the "group of schizophrenias," different forms of schizophrenia that had to be distinguished from each other. Kraepelin believed that some children classified as mentally handicapped actually had schizophrenia. Karl Leonhard (1986) recently identified a very early manifestation of schizophrenia, the so-called early infantile catatonia. Leonhard believes that this form of child-

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hood schizophrenia is regularly misdiagnosed as severe mental handicap.

August Homburger (1926) stated that childhood schizophrenia is characterized by withdrawal, negativism, and strange and unexpected behavior. Today we call these "negative" symptoms. He also stated that delusions are rare, especially in young children. Homburger believed that schizophrenia had at least two manifestations: a slow retarded hebephrenic form with cognitive deterioration and an acute catatonic form.

According to Homburger, children also manifest premorbid characteristics and can be divided into three groups on the basis of these characteristics: (1) children with a *premorbid normal development*, good intellectual functions, and no character anomalies; (2) children with *premorbid mental retardation*; and (3) children who have *normal intellectual functions* but have character anomalies and display some types of strange behavior.

Jakob Lutz (1937, 1938) described childhood schizophrenia as a distinct entity, separate from adult schizophrenia. Leo Kanner (1943) and Hans Asperger (1944) delineated two well-known autistic syndromes—early infantile autism and autistic personality disorder—out of the pool of schizophrenic psychoses. Kanner (1943, 1957) and James Anthony (1962) proposed three groups of psychoses, with and without relationship to schizophrenia, which will be discussed later.

Finally, Leonhard (1986) proposed some ideas that are pertinent to our discussion. First, he believes that we should not speak of schizophrenia, but of the group of schizophrenic psychoses, a group that includes several disorders. A unique etiology of schizophrenia is therefore an illusion. By the group of schizophrenic psychoses, Leonhard does not refer to the traditional subdivisions of hebephrenic, paranoid, catatonic, and so on, but to a special subdivision of schizophrenic disorders consisting of unsystematic and systematic schizophrenias.

Unsystematic schizophrenias and systematic schizophrenias differ in symptoms, course, and prognosis. Unsystematic schizophrenias are characterized by predominantly affective symptoms (e.g., extreme anxiety states, delusions, hallucinations, ideas of reference). The course is acute, sometimes periodic, and has good remissions. Unsystematic schizophrenias have more in common with affective psychoses than with systematic schizophrenias.

Systematic schizophrenias are characterized predominantly by cognitive dysfunctions and disturbances of voluntary functions. The primary dysfunction is in the basic cognitive processes.

Leonhard's systematic schizophrenias have nothing to do with systematic or systematized symptomatology, but with disturbances in the brain that result in a defect. The course is chronic, without recovery to the former cognitive level, and the prognosis is poor. Leonhard argues that the cause may lie in disorders of cerebral systems.

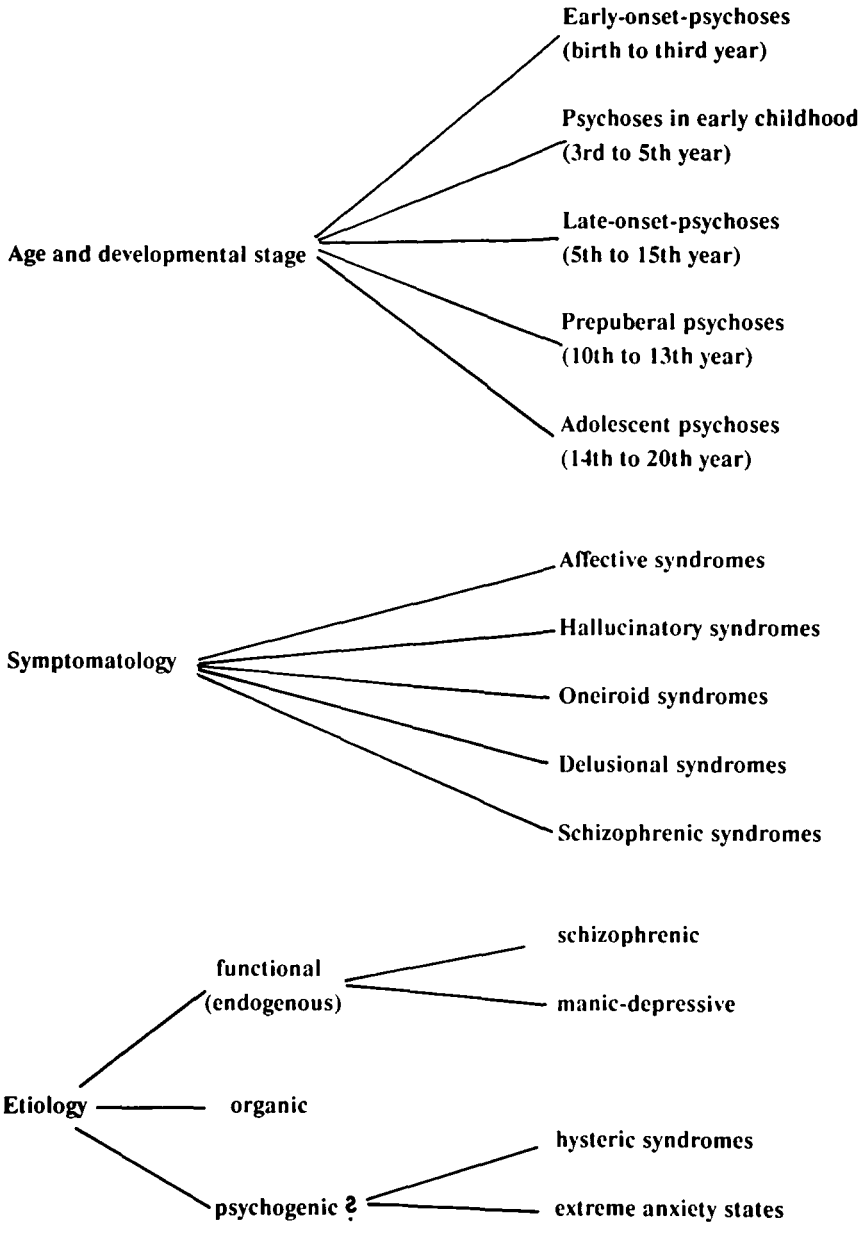
Leonhard distinguishes *early infantile catatonia* as a special form of childhood schizophrenia. The clinical picture is characterized by motor symptoms, absence of language development or very poor language ability, circumscribed intellectual impairments, negativism, (sometimes) periodic course, and predominance of the male sex.

Schizophrenic Psychoses in Childhood and Adolescence

Schizophrenic psychoses in childhood are important but rare disorders within the spectrum of psychoses. They were delineated as specific psychotic disorders only in the late 1930s (Lutz 1937/38). By the 1950s and 1960s, it was evident that age and developmental stage were important criteria for the classification of childhood psychoses (Group for the Advancement of Psychiatry 1966; Stutte 1969). Their importance was demonstrated by several empirical studies (Rutter and Lockyer 1967; Rutter et al. 1967; Kolvin 1971; Kolvin et al. 1971*a*, 1971*b*, 1971*c*, 1971*d*, 1971*e*). Finally, these studies confirmed the notion of Kanner (1943, 1957), who subdivided childhood psychoses into three groups: early infantile autism, childhood schizophrenia, and disintegrative psychoses of childhood. Disintegrative psychoses comprise disorders such as dementia infantilis (Heller 1908) and psychoses related to different kinds of brain damage. These subdivisions have also influenced the multiaxial classification systems of the International Classification of Diseases (ICD–9; World Health Organization 1978) (Rutter et al. 1976), *DSM–III* (American Psychiatric Association 1980), and *DSM–III–R* (American Psychiatric Association 1987). Both *DSM* and ICD differentiate between early infantile autism, childhood schizophrenia, and early childhood dementia.

Figure 1 shows some general criteria for the classification of psychotic disorders in childhood and adolescence. Though classification according to etiologic principles would be preferable, our current knowledge does not allow

Figure 1. General criteria for the classification of psychotic disorders in childhood and adolescence



such a classification. Therefore, modern classification systems base their definitions on the symptomatology of the disorders. In childhood and adolescence, however, age and developmental stage play a very important role in the classification of schizophrenia.

Epidemiology

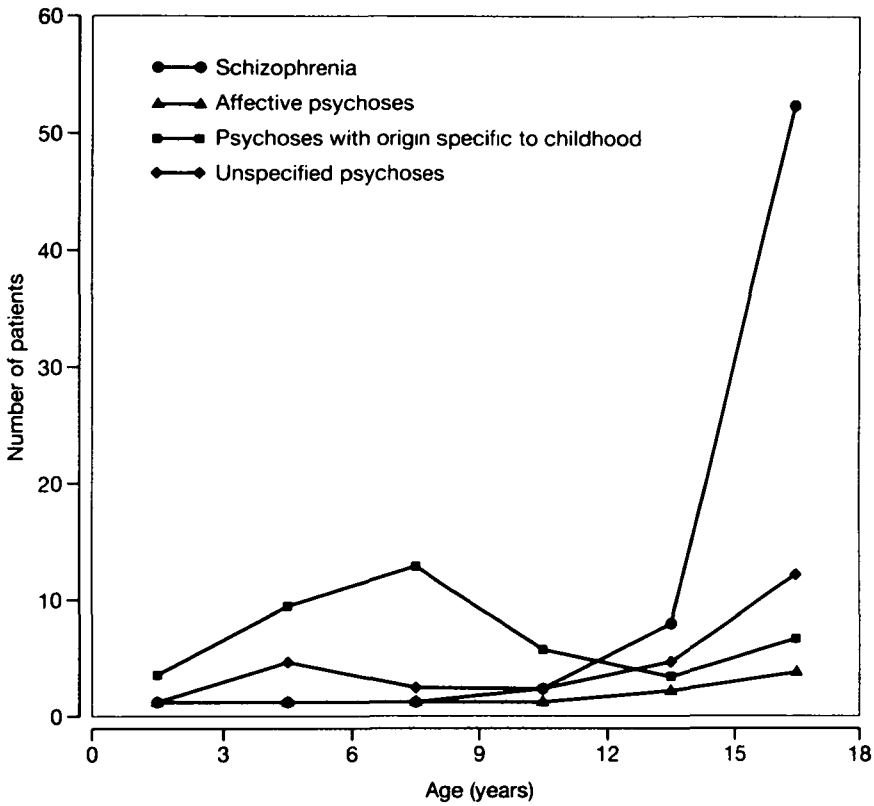
Available epidemiologic data are not reliable because of differences in definition and the fact that several heterogeneous disorders have been subsumed under the heading of "psychoses in childhood." According to Bleuler (1972) and Lutz (1972), about 4 percent of schizophrenic psychoses begin before age 15, and 0.5–1 percent before age 10. In the general population, 1 child in 10,000 will develop a schizophrenic disorder.

Figure 2 shows the age distribution of psychotic disorders in a clinical population of children and adolescents (n = 3,280) in three counties in northern Hessen, Germany, classified according to Rutter et al.'s (1976) multiaxial classification scheme. This sample includes all children and adolescents who sought help from psychiatric or counseling institutions in the three counties (population = approximately 575,000) over a 1-year period. Figure 2 shows the point prevalence of the psychotic disorders at different ages (Remschmidt 1988).

Figure 2 demonstrates clearly that up to age 12, psychotic states are rare conditions, but that after age 13, there is a remarkable increase in the occurrence of schizophrenia.

The same increase was found in a study of 280 children and adolescents with schizophrenia in two independent clinical settings (Würzburg and Marburg). The Marburg epidemiologic sample consisted of 98 of the 3,280 patients from the northern Hessen study. The Würzburg clinical sample comprises 121 inpatients (61 boys and 60 girls), ages 7–21, treated between 1985 and 1990. The Marburg prospective study in-

Figure 2. Age distribution of psychotic disorders in a clinical population of children and adolescents (n = 3,280) in three counties



cluded 61 schizophrenia patients who were treated as inpatients in the Marburg University Hospital or in a rehabilitation program of the same hospital during 1991 and 1992. This sample comprised 32 boys and 29 girls, ages 7–21. Again, all patients were classified as having schizophrenia according to the ICD–9 multiaxial classification scheme. The results of these studies are demonstrated in figure 3, which also shows a remarkable increase in schizophrenia between ages 13 and 17.

The sex distribution in this sample of 280 schizophrenia patients is nearly equal: 144 boys (51.4%) and 136 girls (48.6%). But if we look at the subsamples of two age groups—the very early-onset group (group I, first manifestation before 14) and a second group (group II, first manifestation after 14), we find a very clear predominance of males in group I. The Würzburg clinical study (n = 121) and the Marburg prospective study (n = 61) both had a predominance of males in group I (see table 1).

Table 1 shows two remarkable things. First, the very early-onset schizophrenia group comprises approximately 11 percent of all patients in these two samples. Second, the gender ratio in the very young group is 3:1 in favor of boys. Within the Marburg prospective study, we find a relationship of 4.5:1. We assume that these data are reliable because they are drawn from the only clinical settings specializing in schizophrenia in their respective localities. Presumably nearly all schizophrenia patients would be admitted to these centers.

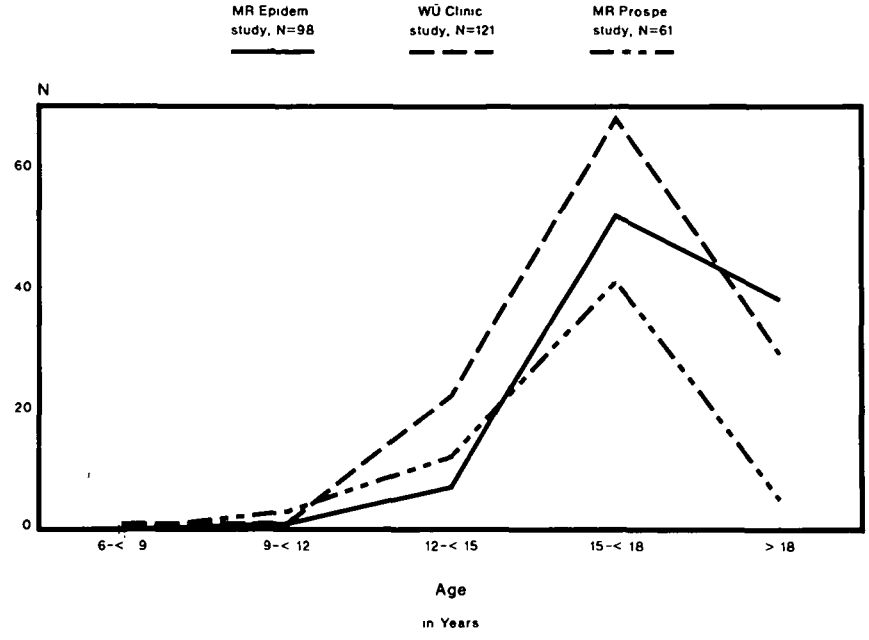
The Importance of Age and Developmental Stage

Several studies have shown that age and developmental stage are the most influential factors in the clinical picture of childhood psychoses (Anthony 1958, 1962; Stutte 1960, 1969; Kolvin 1971; Kolvin et al. 1971*a*, 1971*b*, 1971*c*, 1971*d*, 1971*e*; Werry 1979; Bettes and Walker 1987). Most researchers agree that at least four groups of psychoses in childhood and adolescence can be differentiated by age and developmental stage. This subdivision was first proposed by Anthony (1958, 1962) and is demonstrated in table 2.

The first group of psychoses comprises different psychotic syndromes, all of which have a slow beginning and chronic course, and manifest themselves before the third year of life. Except for early infantile catatonia, they have no connection to schizophrenia.

The second group includes different psychotic states, most of which have an acute beginning and different regressive behaviors that manifest themselves between the third and fifth years of life. The connection with schizophrenia is questionable, again with the exception of the early infantile catatonia described by Leonhard (1986), who believes that a connection to schizophrenia is likely.

Figure 3. Age distribution in childhood and adolescent schizophrenia, calculated from three samples of schizophrenia patients (ages 7–21 yrs, *n* = 280)



The Marburg (MR) epidemiologic study comprised all 98 patients who attended child psychiatric or other counseling and treatment agencies during a 1-year period in three counties in northern Hessen. The Würzburg (WÜ) clinical study included all schizophrenia inpatients between ages 7 and 21 who had been treated between 1985 and 1990 in the Würzburg hospital. The Marburg prospective study included patients from the child psychiatric university hospital and an associated rehabilitation center for children and adolescents with schizophrenia during 1991 and 1992.

The third group of psychoses are the late-onset psychoses of late childhood to prepuberty, which have a fluctuating or subacute course and a clear relationship to schizophrenia of adolescence and adulthood. A good example here is the prepubertal schizophrenia described by Stutte (1969) and Eggers (1973).

In his recent review, Werry (1992) distinguishes between early-onset schizophrenia beginning in childhood or adolescence (before age 16 or 17) and very early-onset schizophrenia (onset before age 13). Werry separates the latter group because that definition is more precise than the term "prepubertal." The age of puberty varies, and most studies that have used the term "prepubertal schizophrenia" have not considered the pubertal stages. Werry states further that a review of the studies of childhood schizophrenia is complicated by the fact that before ICD-9 and *DSM-III*, all psychotic disorders of childhood were aggregated into the single category of childhood schizophrenia. So in many articles it is impossible to differentiate between early infantile

Table 1. Sex distribution of schizophrenia in two groups of patients with manifestation of the disorder before and after age 14

Group	Würzburg clinical study (1985–90)		Marburg prospective study (1991–92)		Both studies		Total patients *n* (%)
	Male *n* (%)	Female *n* (%)	Male *n* (%)	Female *n* (%)	Male *n* (%)	Female *n* (%)	
Group I (< 14 years)	6 (66.7)	3 (33.3)	9 (81.9)	2 (18.1)	15 (75.0)	5 (25.0)	20 (11)
Group II (> 14 years)	55 (49.1)	57 (50.9)	23 (46.0)	27 (54.0)	78 (48.1)	84 (51.9)	162 (89)
Total	61 (50.4)	60 (49.6)	32 (52.5)	29 (47.5)	93 (51.1)	89 (48.9)	182 (100)

Note.—All patients were diagnosed according to the International Classification of Diseases, 9th revision (World Health Organization 1978) multiaxial classification scheme and were treated as inpatients. The Würzburg clinical study comprised all patients who had been hospitalized between January 1, 1985, and December 31, 1992.

Table 2. Psychotic syndromes in childhood and adolescence and their relation to schizophrenia[1]

Clinical syndrome	Age at manifestation and course	Relation to schizophrenia
Group 1 (Anthony 1958, 1962) Autism (Kanner 1943) Pseudodefective psychosis (Bender 1947, 1959) "No-onset" type (Despert 1938)	Early manifestation until third year of life and chronic course	No relation to schizophrenia
Early infantile catatonia (Leonhard 1986)	Manifestation before third year of life possible	Relation to schizophrenia likely
Group 2 (Anthony 1958, 1962) Dementia infantilis (Heller 1908) Dementia praecocissima (DeSanctis 1908) Pseudoneurotic schizophrenia (Bender 1947, 1959) "Acute-onset" type (Despert 1938) Symbiotic psychosis (Mahler et al. 1949; Mahler 1952) Asperger syndrome (Asperger 1944, 1968)	Manifestation between third and fifth year of life with acute course and regressive behavior	Relation to schizophrenia questionable
Early infantile catatonia (Leonhard 1986)	Most frequent manifestation within the first 6 years of life	Relation to schizophrenia likely
Group 3 (Anthony 1958, 1962) Psychoses (late-onset psychoses) (Kolvin 1971) Pseudopsychopathic schizophrenia (Bender 1959)	Late-onset psychoses (late childhood and prepuberty) with fluctuating, subacute course	Relation to schizophrenia of adolescence and also adulthood (Anthony 1958, 1962; Eisenberg 1957; Rimland 1964; Rutter 1967)
Prepuberal schizophrenia (Stutte 1969; Eggers 1973)	Manifestation in prepuberty	Clear relation to schizophrenia
Group 4 Adolescent schizophrenia	Manifestation during puberty and adolescence	Clear relation to schizophrenia

[1]Adapted from Remschmidt 1988.

autism, childhood schizophrenia, and other psychoses.

The fourth group of psychoses is adolescent schizophrenia, which manifests at puberty and adolescence and is clearly related to schizophrenia. Psychoses manifested during adolescence may or may not have precursor symptoms in childhood (Rutter 1967; Remschmidt 1975*a*, 1975*b*). This subdivision according to premorbid personality and psychosocial adaptation also seems to be important in positive and negative schizophrenia in adolescence, because there is a relationship between poor premorbid adjustment and negative schizophrenia in adulthood (Andreasen and Olsen 1982).

The Concept of Positive and Negative Schizophrenia in Children and Adolescents

The concept of positive and negative symptoms in schizophrenia has been widely used in general psychiatry but has rarely been applied to schizophrenia in childhood and adolescence (Remschmidt et al. 1991). We found only one study that applied this concept to childhood schizophrenia. Bettes and Walker (1987) analyzed a sample of 1,084 children with psychotic symptoms that were selected from a total sample of 11,478 children and adolescents, ages 5–18, from all State-supported inpatient and outpatient facilities in Erie County, NY, and the New York

City area. The presence or absence of 31 symptoms, including psychotic symptoms, was recorded at intake by a psychiatrist, a psychologist, or a social worker. The authors found a strong effect of age on the manifestation of positive and negative symptoms. Positive symptoms increased linearly with age, while negative symptoms occurred most frequently in early childhood and late adolescence. This was true for both the total sample of children and the subsample of children with psychotic diagnoses. Bettes and Walker found few sex differences and a correlation between symptoms and IQ: children with high IQs showed more positive and fewer negative symptoms than low-IQ children.

Bettes and Walker (1987) offered three interpretations of their results.

1. Positive and negative symptoms may represent different psychiatric conditions with different underlying causes. This association has been proposed by Crow (1980) for adult schizophrenia.
2. The two symptom types may be associated with different stages of the course of schizophrenia. For instance, negative symptoms could be associated with advanced stages of the disorder. But, as the authors state, this interpretation does not explain the simultaneous increase of both positive and negative symptoms during adolescence.
3. Finally, "the clinical manifestation of psychosis in the vulnerable child varies as a function of environmental demands as well as characteristics of the individual. Positive symptoms, particularly those that are based on ideational excess (e.g., paranoia, delusion, grandiosity), may increase in likelihood as cognitive capacity increases. This would explain the linear increase in positive symptoms with age, as well as the lower rate of positive symptomatology in low-IQ children. Alternatively, positive symptoms may be subserved by certain biochemical processes that are triggered during puberty" (p. 565).

In our prospective study of 61 patients divided into two groups (group I: very early onset, < 14 years; group II: first manifestation of schizophrenia > 14 years), we could demonstrate some differences in negative and positive symptoms between these two groups. The distribution of *DSM–III–R* types by age at onset is as follows:

- Paranoid: 63.6 percent (n = 7) with onset < 14; 68 percent (n = 34) with onset > 14.
- Disorganized: 27.3 percent (n = 3) with onset < 14; 18 percent (n = 9) with onset > 14.
- Schizoaffective: 8 percent (n = 4) with onset < 14.
- Undifferentiated type of schizophrenia: 9.1 percent (n = 1) with onset < 14; 2 percent (n = 1) with onset > 14.
- Schizophreniform disorder: 2 percent (n = 1) with onset > 14.
- Residual type of schizophrenia: 2 percent (n = 1) with onset > 14.

These 61 patients received the following neuroleptic medications:

- 24 patients (39.3%) were treated with the atypical neuroleptic clozapine and 1 patient (1.6%) received zotepine.
- 17 patients (27.9%) received haloperiodol.
- 23 patients (37.7%) were treated with phenothiazines (fluphenazine, levomepromazine, promethazine, propylphenothiazine, thioridazine, perphenazine).
- 10 patients (16.4%) received thioxanthenes (flupentixol, chlorprothixene).

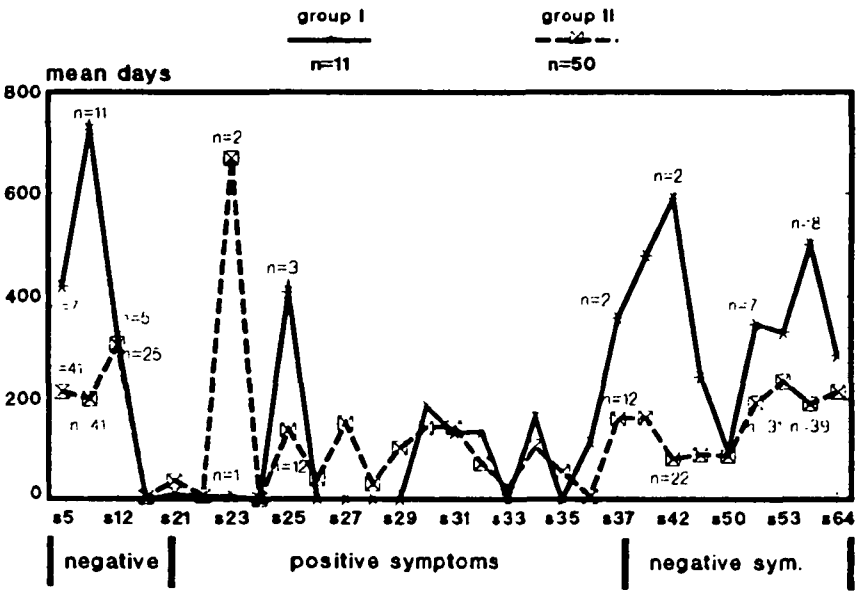
In addition to pharmacologic treatment, all 61 patients were integrated into a structural therapy program including supportive psychotherapy, family-oriented therapy, and social and cognitive training programs.

To get information about positive and negative symptoms and other precursors of schizophrenia, we administered the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS), a semistructured interview that allows for the retrospective assessment of schizophrenia and other symptoms before the first manifestation of schizophrenia. This instrument was developed by Häfner and his group (Häfner et al. 1990) and modified to investigate children and adolescents and their parents. Experienced child psychiatrists used the IRAOS instrument to interview parents; the instrument also used all information that could be obtained from the records. The interrater reliability of the IRAOS was found to be satisfactory, with kappa values 0.62–1.00 (Häfner et al. 1992).

Figure 4 demonstrates the negative and positive symptoms before the manifestation of schizophrenia for the two groups. There is at least a trend for group I to show a longer "precursor time" of negative symptoms than group II.

The same tendency is demonstrated in figure 5, which shows the cumulative frequency of positive and negative symptoms before the index admission. While many patients show both negative and positive symptoms before the in-

Figure 4. Positive and negative symptoms in two subgroups of schizophrenia patients with first manifestation < 14 (group I) and > 14 (group II)



Negative Symptoms

5 poor concentration
9 social withdrawal
12 anergia and retardation
13 loss of libido
41 increased distractibility
42 disturbance of affect
44 disturbance of speech
50 self-care
52 underactivity
53 slowness
54 social withdrawal
64 loss of interest

Positive Symptoms

21 thought disorder
22 thought insertion
23 thought broadcast
24 thought echo
25 thought block and withdrawal
26 auditory hallucinations
27 verbal hallucinations
28 visual hallucinations
29 other hallucinations
30 delusions of control
31 delusions of reference
32 delusions of persecution
33 expansive delusions
34 delusions of influence
35 primary delusions
36 delusions concerning appearance
37 other delusions

Symptoms were investigated retrospectively through the semistructured Instrument for the Retrospective Assessment of Onset of Schizophrenia (IRAOS; Häfner et al. 1990).

dex admission, both categories of symptoms become more frequent and converge at the time of the index admission.

These investigations underline the findings in earlier studies that age and developmental stage are decisive variables for the symptomatology of schizophrenic states in childhood and adolescence. This seems to be true at least for the very early-onset group.

Introversive and Extraversive Precursor Symptoms of Child and Adolescent Schizophrenia

We developed a checklist of premorbid symptoms that could be classified as either "introversive" or "extraversive." Examples of introversive symptoms are mutism, mental slowness, social isolation, general anxieties, specific anxieties, and obsessive-compulsive symptoms. The extraversion dimension comprised items such as hyperactive and dissocial behavior, aggression, and school refusal.

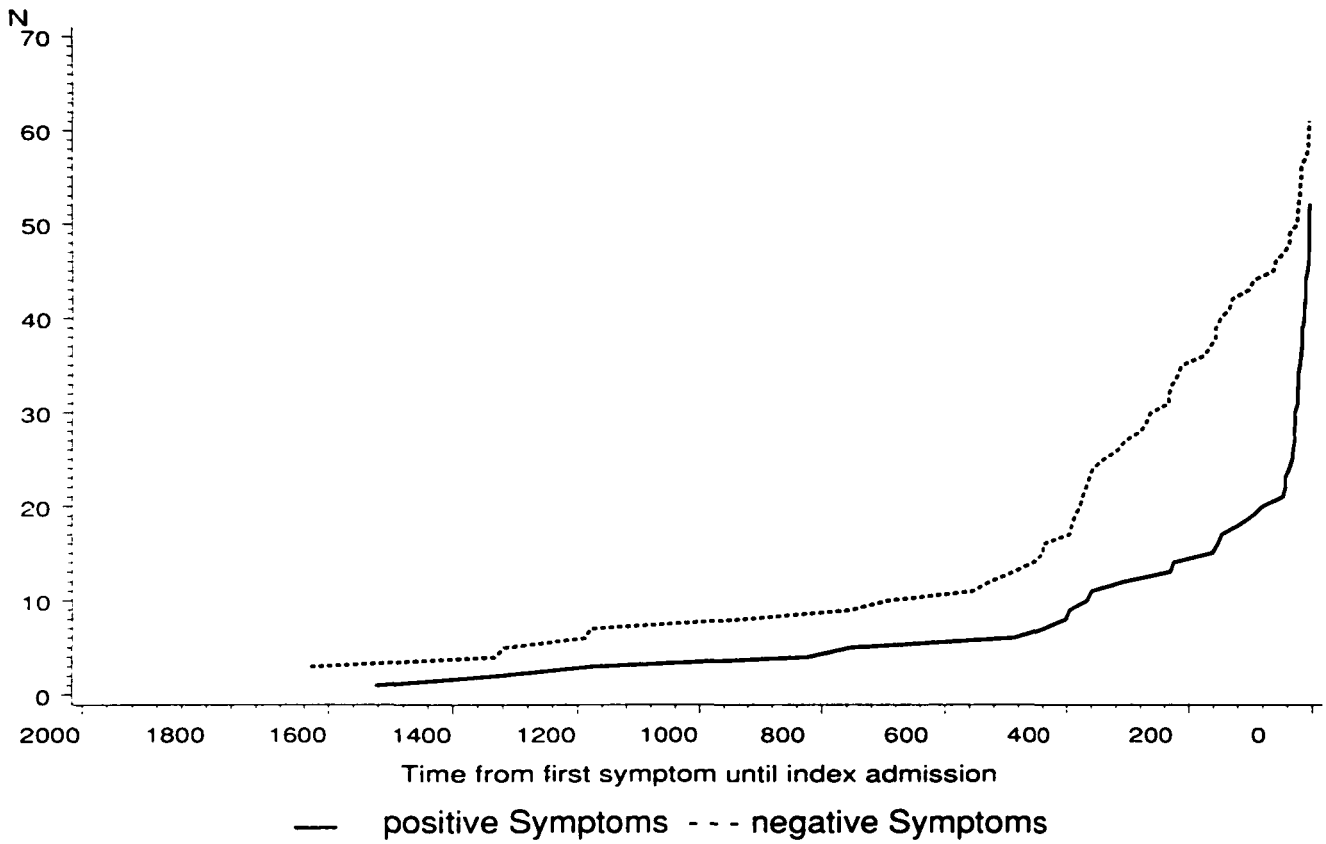
According to this categorization, there was no significant difference between the two groups (Fisher's exact test, $p = 1.00$). However, we found more introversive than extraversive symptoms in both age groups (χ^2 test: $p = 0.0008$).

Other Premorbid Characteristics

We also used a symptom checklist to classify children according to four groups of premorbid disturbances: developmental disorders, conduct disorders, learning disabilities, and emotional disorders. In all cases, we tried to get information on premorbid behavior through a careful analysis of the case histories and through information from parents.

We found no remarkable differences between groups I and II. There was a general trend for developmental disorders to appear first, followed by conduct disorders, emotional disorders, and

Figure 5. Retrospective assessment of positive and negative symptoms in 61 children and adolescents with schizophrenia



The semistructured Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner et al. 1990) was used. The first admission is marked by 0. The units for the time axis are days.

learning disabilities. This is demonstrated in figure 6.

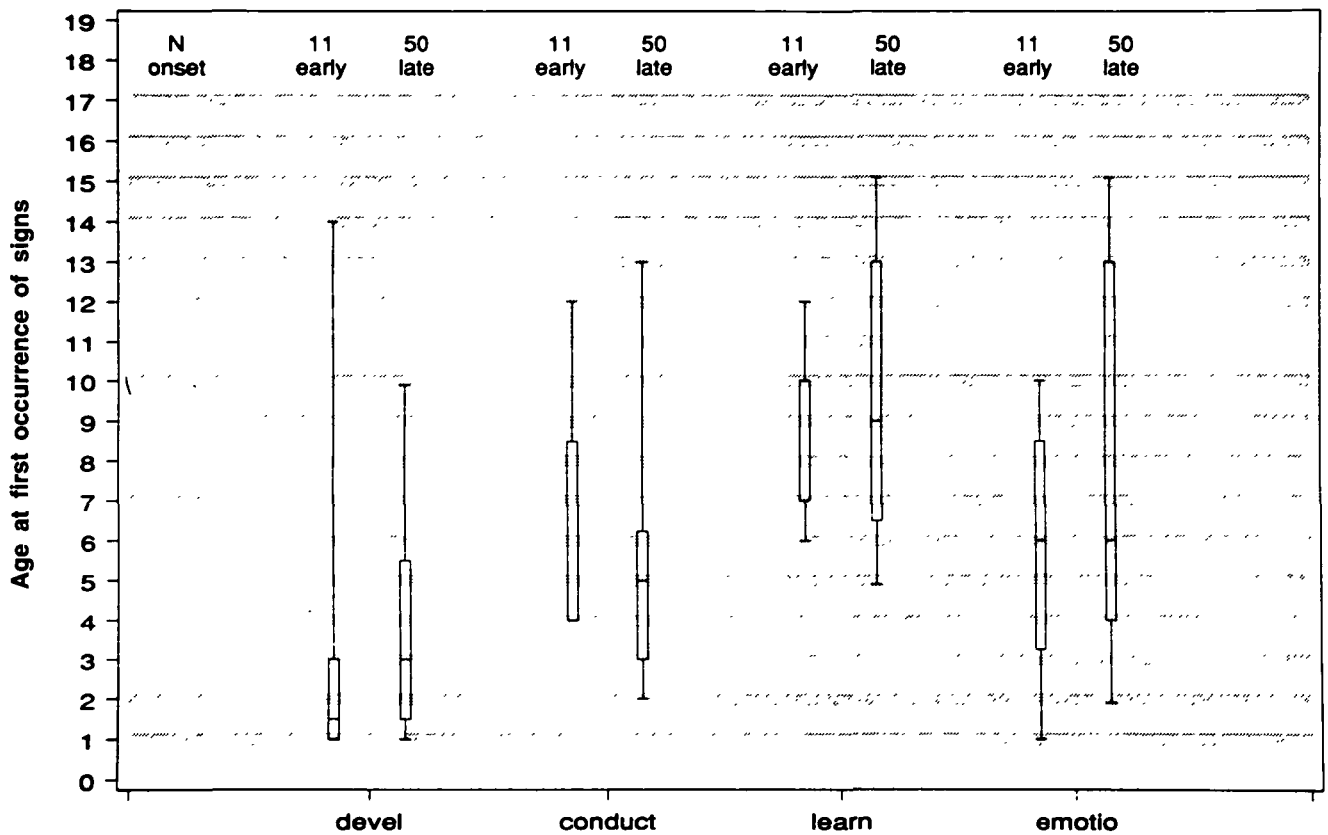
Etiology

Four factors are discussed in relation to etiology: genetic influences, organic influences, environmental influences, and multifactorial concepts.

Genetic. The risk of schizophrenia in a child with one parent with schizophrenia varies from 9 to 16 percent. If both parents have schizophrenia, the risk of schizophrenia increases to between 40 and 68 percent. The concordance rates of monozygotic twins vary between 20 and 57 percent and those of dizygotic twins between 5 and 16 percent (Zerbin-Rüdin 1985). Adoption studies have confirmed a strong genetic influence, but they have also shown that environmental influences are of great importance. Several high-risk studies in children of parents with schizophrenia have also demonstrated that genetic and environmental influences are of great importance and interact to some extent. Some of the high-risk studies were designed to identify protective factors that could prevent a schizophrenic disorder in predisposed children (Mednick and Schulsinger 1980).

Organic. Organic influences have also been found in many children who have schizophrenia and may play an important role. Organic findings range from neurologic soft

Figure 6. Comparison of schizophrenia patients with onset < 14 (*n* = 11) and > 14 (*n* = 50)



First psychopathologic signs were assessed retrospectively by an interview with the parents and by using all information from the records. A symptom checklist was used to distinguish four groups of premorbid disturbances: developmental disorders (devel), conduct disorders (conduct), learning disabilities (learn), and emotional disorders (emotio). Box plot: 5th, 25th, 50th, 75th, and 95th percentiles (from the bottom to the top).

signs (Kolvin et al. 1971*e*) and electroencephalographic abnormalities (Kolvin et al. 1971*e*; Itil 1978) to a lowered habituation ability (Mednick and Schulsinger 1980) and various neuropsychological dysfunctions (Asarnow et al. 1986; Fish et al. 1992). These and other results have led to the hypothesis that pre-, peri-, or postnatal hypoxia may be important in the genesis of childhood schizophrenic disorders. The limbic system (hippocampus and amygdala) may be especially sensitive to hypoxic influences (Eggers 1985) in that this system is responsible for the coordination of emotions. A dysfunction in this system could cause schizophrenic symptoms such as illusions and hallucinations. The dopamine theory of schizophrenia also falls in line with these considerations.

Environmental. Environmental influences have been discussed widely in relation to the etiology of schizophrenia. Three factors have been considered: individual characteristics of personality, life events, and family influences.

Personality. About 50 percent of children and adolescents with schizophrenia show an uncharacteristic symptomatology in their premorbid personality (Stutte 1969). They have been described as withdrawn, shy, introverted, sensitive, and anxious. It is not clear whether these personality characteristics directly predispose them to schizophrenia or whether they enhance the vulnerability of those children to adverse experiences in general.

Adverse life events. Some evidence indicates that adverse life

events such as the death of a parent, divorce, rejection of the child by the parents, an overly close bonding to the mother, and other unfavorable personal experiences may trigger the development of a schizophrenic disorder (Rabkin 1980; Day 1981; Dohrenwend and Egri 1981).

Family influences. Although the relation of family influences to schizophrenia has been discussed widely, it is not clear that different family theories, such as the "double-bind concept," are specific to the disorder. But there is still some evidence that the following family variables are important either for the first manifestation of the schizophrenic disorder or for a relapse: (1) a deviant style of communication (Doane et al. 1981); (2) a negative style of affective communication within the family (Doane et al. 1981); and (3) a high amount of expressed emotion within the family (Brown et al. 1972; Vaughn and Leff 1976).

All of these influences may be found in families with children or adults who have schizophrenia (see Asarnow et al. 1994, this issue).

Multifactorial Concepts. Those concepts attempt to integrate the different components into a model for the etiology of schizophrenia. A dysregulation of information processing, the central deficit within such a model, has been postulated to have different causes: organic (infections, hypoxia), intrapsychic (personality, ego structure), genetic, and family and psychosocial (deviant communication, expressed emotion, lower social class, adverse life events). It has been postulated that the system for the selection and processing of information may be located within the limbic system. If, for whatever reason, this information-processing system becomes deficient, these children or adolescents are at risk for schizophrenic disorders, especially if they have a genetic predisposition or adverse life events and unfavorable family conditions (Remschmidt 1988).

Therapy and Rehabilitation

With regard to therapy of schizophrenic psychoses in children and adolescents, five different aspects must be integrated (Remschmidt and Martin 1992): (1) pharmacologic treatment of acute psychotic states, (2) pharmacological prevention of relapses, (3) psychotherapeutic measures, (4) family-oriented measures, and (5) specific measures of rehabilitation.

Pharmacologic Treatment of Acute Psychotic States. During acute states of schizophrenia, neuroleptic treatment is absolutely necessary. In cases with acute symptoms (hallucinations and delusions, extreme excitement), butyrophenones (especially haloperidol and benperidol) and phenothiazines (fluphenazine and perphenazine) have been very useful. In more chronic cases, less potent neuroleptics such as propylphenothiazine and thioridazine have been useful. In cases of extreme excitement and aggression, a combination of these substances with levomepromazine and chlorprotixene has been effective. In patients with predominantly negative symptoms, clozapine trials have been encouraging. However, clozapine requires systematic monitoring of blood counts, because agranulocytosis has been observed in several cases.

Remschmidt et al. (1992) reported on their early and recent studies on clozapine in adolescents. The first study, carried out by Siefen and Remschmidt in 1986, comprised 21 patients, 12 of whom were age 18. The indications for clozapine were insufficient response to other neuroleptic agents, likelihood of psychotic symptoms, chronicity, and extensive extrapyramidal side effects from the neuroleptic agents. The patients had an average of 2.4 inpatient hospitalizations and had received an average of 2.8 different antipsychotics without adequate therapeutic response. Clozapine was administered over an average of 133 days at an average maximum dosage of 415 mg/d (range = 225–800 mg/d) and an average maintenance dosage of 363 mg/d (range = 150–800 mg/d). Marked improvement or complete disappearance of most of the remaining psychopathologic symptoms was seen in 11 of 21 subjects (52%), and at least some improvement was seen in an additional 6 subjects (29%). Vegetative side effects such as daytime weariness, dizziness, orthostatic hypotension, and hypersalivation were usually transient. Deviations from the norm were of no clinical significance and no more frequent than with other neuroleptic agents, and the values returned to normal when treatment was continued. Siefen and Remschmidt conclude that clozapine is a useful addition to the group of neuroleptic drugs available for the treatment of adolescent schizophrenia.

Remschmidt et al. (1992) reported on a retrospective and a prospective study with clozapine in adolescent schizophrenia. Forty-one adolescent patients with ICD–10 (World Health Organization

1992) diagnoses of schizophrenia (mean age = 18.2 yrs, range = 13–22 yrs) were treated with the atypical neuroleptic clozapine (mean dosage = 330 mg/d, range = 50–800 mg/d). These patients met the following criteria:

1. Nonresponse to conventional neuroleptic medication, including at least two neuroleptic drugs, usually haloperidol and fluphenazine: 35 patients (85.4%).
2. Deterioration of symptomatology under pretreatment with typical neuroleptics: 19 patients (46.3%).
3. Extreme side effects under conventional neuroleptic treatment: 18 patients (43.9%).

The most common side effects of typical neuroleptic treatment were dyskinesias and akathisia, which occurred in about 52 percent of these patients. Severe cholinergic side effects with atonia of the bowel and cord bladder occurred in about 15 percent of the sample in pretreatment conditions. Therefore, clozapine treatment was indicated by clinical nonresponse, worsening of symptoms, and severe side effects under conventional treatment strategies. To minimize the risk of agranulocytosis, clozapine was administered after a careful analysis of each case in a consensus conference, and all requirements of the guidelines for clozapine treatment were strictly fulfilled. The 41 patients receiving clozapine had an average duration of schizophrenic disorder of 3.3 years. The results are described below:

In seven patients (17.1%), clozapine had to be interrupted because of severe side effects. After two weeks of 100 mg/d of clozapine in combination with carbamazepine (400 mg/d), one patient developed a severe worsening of symptoms with stupor. After 2 weeks of clozapine (250 mg/d), one patient developed a beginning ileus. In two patients clozapine was discontinued because of leukopenia (2.9 and 2.5/nL) without agranulocytosis. In two other patients, hypertension, tachycardia, and electrocardiographic abnormalities occurred. In one case, liver enzymes (GOT and GPT) rose to 10 times the normal values. Three patients (7.3%) did not respond to clozapine. A total of 10 schizophrenia patients (24.4%) of the 41 treated with clozapine did not benefit from this atypical neuroleptic.

A remarkable improvement of schizophrenic symptoms was seen in 31 (75.6%) of the 41 schizophrenia patients who did not respond to conventional neuroleptics or who showed worsening of symptoms and side effects under conventional neuroleptic drugs. The majority of these patients were able to participate in a comprehensive rehabilitation program, and 3 (7.3%) showed complete remission. Further, it was evident that clozapine was more effective in Type I schizophrenia than in Type II schizophrenia. The rate of improvement of the positive symptoms was approximately 65 percent. Clozapine was especially effective for delusions, hallucinations, positive thinking disorders, excitement, and attention. Clozapine was not as effective with negative symptoms. Symptoms such as anhedonia, affective flattening, and autistic behavior could not be improved significantly. But clozapine was somewhat effective in reducing symptoms such as anergia (up to 11%), mute behavior (14%), bizarre behavior (22%), and thought blocking (22%).

The results of the ongoing prospective study, whose design was described in Remschmidt et al. (1992), are not yet available. Birmaher et al. (1992) recently reported three cases of adolescent schizophrenia patients (two 17-year-old boys and one 18-year-old girl) who had been successfully treated with clozapine dosages of approximately 300 mg/d.

Pharmacologic Prevention of Relapses. In childhood and adolescence, chronic schizophrenic psychoses require treatment with neuroleptic depot medication. Haloperidol decanoate, fluphenazine decanoate, and fluspirilene have been used successfully for this purpose. If the medication is given as an intramuscular injection, the dose should usually be low. Relapses of acute psychiatric symptoms can be prevented with this approach. Relapse prevention is particularly important during adolescence, when patients have not yet finished school or professional training.

Psychotherapeutic Measures. The first task of all psychotherapeutic measures in childhood and adolescent schizophrenia is to present clear information about the disorder and the related problems to patients and their parents. All other psychotherapeutic measures should be supportive and less conflict producing than this initial task. The patient must learn to cope with emotional stress in a way that prevents relapses and exacerbation of symptoms. Finally, training programs dealing with the basic cognitive deficits in adolescents with schizophrenia have also been effective. Psychotherapy must also consider secondary sequelae of the psychotic process and their effects on patients and families.

Family-Oriented Measures. Clearly, the family must be included in the therapy of children and adolescents with schizophrenic psychoses. However, empirical research has shown that many of the ambitious concepts of family therapy propagated during the last two decades have not fulfilled their promises. Although there is clearly no typical "psychotic family," studies using the concept of expressed emotions in adults have shown that emotional factors within the family may play an important role in relapses of the disorder. Therefore, a decision as to the family's involvement in the therapeutic process must be made for every child or adolescent with schizophrenia. The extent of family involvement depends on the patient and the disorder, the structure and stability of the family, and the experience of therapists in dealing with these children and families.

Our research has shown three levels of family intervention to be useful: family counseling, supporting and structuring family therapy, and extended development-oriented family therapy. In our experience, structural therapy programs such as those described in table 3 can reduce the level of emotional stress for the schizophrenia patient. Depot neuroleptic medication, on the other hand, may preserve the patient from extreme reactions to environmental stress.

Table 3. Cooperation with families of children and adolescents with schizophrenic disorders according to Mattejat 1989

Level of intervention	Focal problem	Intervention aims	Typical methods
Family counseling	Information deficits, discouragement, frustration, feelings of insecurity, vague feelings of guilt	Development of stable therapeutic alliance	Orientation and security through information, positive connotation
Supporting and structuring family therapy	Escalative circles between patient's symptoms and family interaction	Neutralization and control of symptoms, disconnection of causal links between family interaction and patient's symptoms (interruption of secondary dynamics)	Clear agreements and determinations, behavior contracts ("direct" interventions)
Extended development-oriented family therapy	Relationship patterns and family conflicts that inhibit development	Extension of scope of decisions and actions, realization of developmental options	Reframing, paradox and provocative methods ("indirect" methods), conflict negotiation, nonverbal and action methods

Specific Measures of Rehabilitation. Approximately 40 percent of children and adolescents with schizophrenia need a rehabilitation program after the treatment of their acute episode. This group of patients is not able to continue with school or professional training immediately after discharge from the hospital. We have set up a rehabilitation program to help these patients over a period of 1 or 2 years. The program has been described elsewhere (Martin and Remschmidt 1983, 1984), and a recent evaluation (Martin 1991) has shown that a stepwise reintegration of most patients into school, professional training, and family is possible.

Prognosis and Outcome

Few studies have dealt with the prognosis of adolescents with schizophrenia. According to Weiner (1982), the prognosis of schizophrenia beginning in prepuberty and adolescence is unfavorable compared with schizophrenic disorders with a first manifestation in adulthood. About the same rate of adolescents and adults with schizophrenia reach full remission (23% vs. 25%), but only 25 percent of adolescent-onset schizophrenia subjects achieve partial remission, compared with about 50 percent of adult schizophrenia patients. Finally, a chronic course can be observed in 52 percent of adolescent

schizophrenia subjects, compared with 25 percent in adults.

Some conclusions can be drawn from various followup studies (Remschmidt 1988). First, schizophrenic psychoses with manifestation before age 10 have a poor prognosis (Annell 1963; Eggers 1967). This also applies to schizophrenic psychoses beginning before age 14 (very early-onset psychoses), as demonstrated by our prospective study. The course of both groups was classified according to the criteria of *DSM–III–R* and ICD–10. Table 4 shows that nine patients in group I show a chronic course, with only one characterized as subchronic and one as chronic with acute exacerbations. Table 5 (ICD–10 criteria) shows that all 11 patients can be classified as having a continuous course. The picture is different in group II, but it is still remarkable that 78 percent of the patients in group II can be classified as subchronic or chronic according to *DSM–III–R* criteria and 56 percent as having a continuous course, according to ICD–10 criteria.

Second, patients with acute manifestation of their disorder and with productive schizophrenic syndromes such as hallucinations and delusions (positive symptoms) have a better prognosis than those with a slow onset and with continuous impairment of cognitive functions and/or depressive states. This was demonstrated in our own study of 113 adolescent schizophrenia subjects (58 males, 55 females; mean age = 18.3 ± 2 yrs; mean duration of inpatient treatment = 4 mo), who had been classified according to their symptoms as Type I schizophrenia, Type II schizophrenia, and mixed-type schizophrenia at the beginning and at the end of their inpatient treatment episode (Remschmidt et al. 1991). This classification was carried out by an experienced child psychiatrist using a rating scale based on Andreasen's (1982) criteria. Type I schizophrenia (positive schizophrenia) was defined by a predominance of positive symptoms (e.g., hallucinations, delusions, and pressure of speech). Type II schizophrenia (negative schizophrenia) was characterized by a high frequency of

Table 4. Classification of the course of schizophrenia according to *DSM–III–R* criteria in two groups of schizophrenia patients with onset before (Group I) and after (Group II) age 14

DSM–III–R classification of course	Group I		Group II		Total patients	
	n	(%)	*n*	(%)	*n*	(%)
0.00 Unspecified	0	(0)	5	(10)	5	(8)
0.01 Subchronic	1	(9)	10	(20)	11	(18)
0.02 Chronic	9	(81)	29	(58)	38	(62)
0.03 Subchronic with acute exacerbation	0	(0)	1	(2)	1	(1)
0.04 Chronic with acute exacerbation	1	(9)	2	(4)	3	(4)
0.05 In remission	0	(0)	3	(6)	3	(4)
Total	11	(100)[1]	50	(100)	61	(100)[1]

Note.—*DSM–III–R* = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., revised (American Psychiatric Association 1987).

[1]Total does not add to 100 percent because of independent rounding.

Table 5. Pattern of course according to the ICD–10 criteria in two groups of schizophrenia patients with onset before (Group I) and after (Group II) age 14

ICD–10 pattern of course	Group I		Group II		Total patients	
	n	(%)	*n*	(%)	*n*	(%)
0.00 Continuous	11	(100)	28	(56)	39	(63)
0.02 Episodic with stable deficit	0	(0)	1	(2)	1	(1)
0.03 Episodic remittent	0	(0)	2	(4)	2	(3)
0.04 Incomplete remission	0	(0)	9	(18)	9	(14)
0.05 Complete remission	0	(0)	1	(2)	1	(1)
0.09 Period of observation, less than 1 yr	0	(0)	9	(18)	9	(14)
Total	11	(100)	50	(100)	61	(100)[1]

Note.—ICD–10 = International Classification of Diseases, 10th ed (World Health Organization 1992).

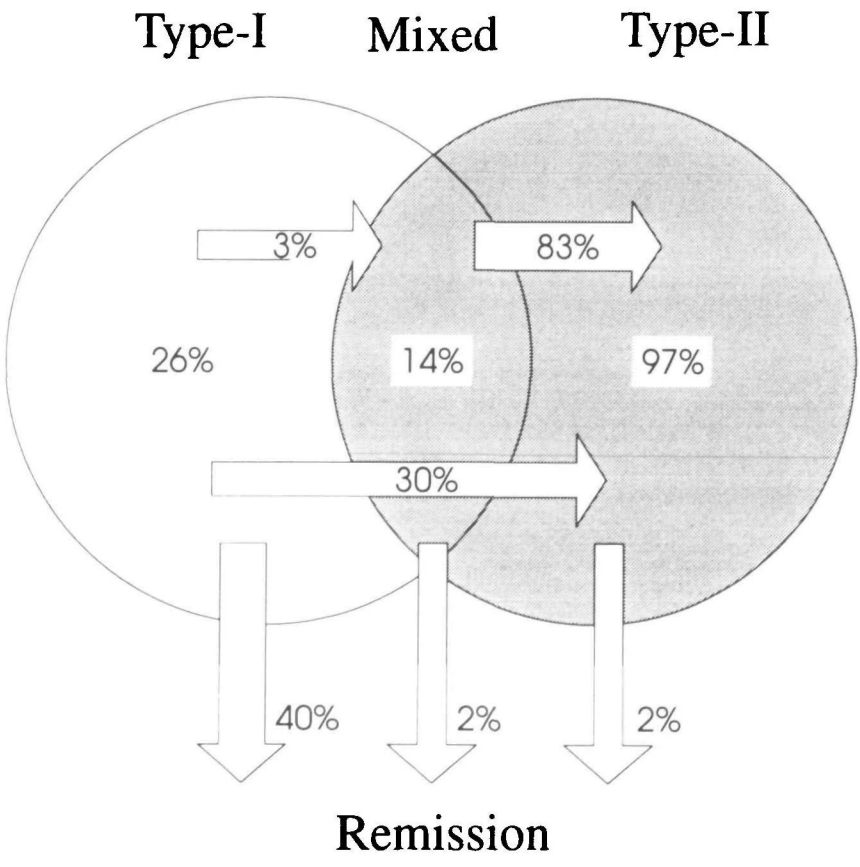
[1]Total does not add to 100 percent because of independent rounding.

negative symptoms (e.g., affective flattening, anergia, and anhedonia). The mixed type (Type III) was diagnosed in all patients in whom both positive and negative symptoms were present and it was not possible to distinguish which of the two symptom categories predominated.

The sample of 113 patients with adolescent schizophrenia was drawn from a total of 1,351 patients visiting the Marburg child psychiatry department between January 1, 1983, and December 31, 1988. All schizophrenia patients were diagnosed according to the multiaxial classification scheme based on ICD–9 (Rutter et al. 1976). The most frequent diagnosis was the paranoid type of schizophrenia (295.3) (n = 52), followed by the hebephrenic type (295.1) (n = 35) and the schizoaffective type (295.7) (n = 17). The rest of the sample consisted of three patients with acute schizophrenic episodes (295.4), three with residual schizophrenia (295.6), two with catatonic type (295.2), and one with a simple type of schizophrenia (295.0).

Figure 7 shows a comparison of the three types of schizophrenia at the beginning and end of the episode. It should be noted that the sample was rather mixed, including patients with first manifestation of schizophrenia and others who had already been hospitalized several times. We always examined the last episode of each patient

Figure 7. Symptom shift in adolescents with schizophrenia between the beginning and end of inpatient schizophrenic episode



The sample comprised patients with first manifestation of schizophrenia and others who had been hospitalized several times (Remschmidt 1993). The figure always includes the last schizophrenic episode observed for each patient within 6 years from 1983 to 1988.

within the 6 years from 1983 to 1988.

Of the 30 patients that belonged to Type I at the beginning, 40 percent (n = 12) went into remission, 26 percent (n = 8) remained Type I, 30 percent (n = 9) shifted to Type II, and 3 percent (n = 1) shifted to the mixed type.

As to Type II schizophrenia, only one patient (2%) was remitted at the end of the episode, none shifted over to Type I, and the remaining 97 percent (n = 34) stayed as Type II. Finally, of the 48 patients whose symptomatology had been classified at the beginning as mixed type, only 1 (2%) went into remission, and 7 (14%) remained in the mixed-type class; the rest (40 patients; 83%) shifted over into Type II schizophrenia. These are not optimistic results, but many patients had already been hospitalized several times; in other words, they had become chronic.

The premorbid personality is also of great importance in outcome. Patients who were socially active, intelligent, and well-integrated children and adolescents in the premorbid phase have a better prognosis than those who were cognitively impaired, shy, introverted, and withdrawn before the manifestation of their schizophrenic disorder (Remschmidt et al. 1988; Martin 1991).

Finally, the prognosis is better in patients without any family load of schizophrenia, with good cooperation with the family, and with rapid improvement during inpatient treatment (Weiner 1982).

Conclusions

Schizophrenic disorders in childhood are very rare, but the number increases remarkably after the beginning of puberty. It is questionable whether several psychotic syndromes of early childhood are related to schizophrenia, but it is clear that there is a prepubertal group that shows this connection and a still earlier one called "early infantile catatonia." Age and developmental stage are important factors that influence symptoms, course, and outcome. As to sex distribution, there is evidence for a male preponderance in the very young group (manifestation < 14) that does not apply for adolescents over age 14.

Therapeutic measures comprise pharmacologic treatment of acute psychotic states, pharmacologic prevention of relapses, psychotherapeutic measures, family-oriented measures, and specific measures of rehabilitation.

As to outcome, patients whose schizophrenic psychoses manifest themselves before age 14 have a poor prognosis. Patients with acute onset and with productive schizophrenic syndromes have a better prognosis than those with a gradual onset and continuous impairment of cognitive functions. The patient's premorbid personality is of great importance: patients who were cognitively impaired, shy, introverted, and withdrawn before the beginning of their psychotic state have a poor prognosis.

Prospective followup studies are necessary to answer the many questions remaining about schizophrenic states in childhood and adolescence.

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