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Age at Onset in Subtypes of Schizophrenic Disorders

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Abstract

Age at onset and sex differences in the age at onset were investigated in the schizophrenic subtypes of 200 patients. Significant differences in the age at onset were observed among these subtypes; the disorganized subtype demonstrated the earliest and the paranoid the latest onset. The mean age at onset of all female patients was significantly greater than that of the male. Specifically, in the paranoid subtype the onset for men occurred earlier than for women. Conversely, in the disorganized subtype the disorder appeared earlier in women. There was no significant sex difference in the age at onset in the undifferentiated and the residual subtypes. In the paranoid subtype most men developed the disease before age 30 (72%), whereas women had an even distribution of the onset before and after 30. Ninety-six patients admitted for the first time demonstrated findings similar to those of the total sample. The data provide additional information on the phenotypic expression of the subtypes of schizophrenic disorders and indicate the necessity for further demographic and genetic studies to delineate the underlying defect.

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Although the heterogeneity of schizophrenia's cause, clinical picture, and prognosis is well established (Cancro 1985), the underlying nature of this heterogeneity with respect to biological, psychological, and social aspects remains uncertain.

Among the factors that may contribute to our understanding of the heterogeneity in schizophrenia are the gender differences reported in the literature, which refer to brain morphology and functioning, to neurochemistry, to family transmission, to premorbid functioning, course and prognosis, and to clinical phenomenology (Goldstein and Tsuang 1990).

It has been hypothesized that the gender differences may be associated with or caused by the following: (1) hormonal differences between men and women, such as the "protective effect" of estrogens and the "triggering" of androgens, which may lead to a greater vulnerability in the male gender (Seeman 1985; Seeman and Lang 1990); (2) differences in brain morphology, conceptualized as a form of the existing sexual dimorphism (Lewine et al. 1990); and (3) diverse cultural and social factors that lead to stressful experiences earlier for men than for women (Loranger 1984). None of these hypotheses, however, has been widely accepted as the cause of the existing variability in schizophrenia.

One of the most consistent findings in the gender differences is the earlier onset of the schizophrenic disorders in men than women (Noreik and Ødegaard 1967; McCabe 1975; Lewine 1980; Loranger 1984; Goldstein et al. 1990; Gureje 1991). It has been estimated (Loranger 1984) that in Bleuler's (1911/1950) classic study of dementia praecox the mean age at onset of the male patients was 3.7 years earlier, whereas in the

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cases reported by Kraepelin (1919/1971) the mean age at onset of the male schizophrenia patients was 2.2 years earlier. Also, in the cases reported by Bleuler (1911/1950), more male patients became ill before the age of 30, whereas more female patients showed the disorder after that age.

A critique about the early studies was that the reported difference in the age at onset was due to diagnostic misclassification, in which affective disorders were included among schizophrenic disorders (Goldstein and Link 1988). More recent studies, however, using well-defined diagnostic criteria, verify the existence of a difference in the age at onset between male and female patients. Further, the sex differences in the age at onset cannot be attributed to an earlier hospitalization of the male patients (Raskin and Golob 1966), since the time of the first hospitalization for schizophrenia is very close to the time of first symptoms reported by the patients' relatives (Kramer 1978; Loranger 1984).

Among the more recent papers, Loranger (1984) reported that the mean age at onset of schizophrenia in men was approximately 5 years earlier than that of women. Also, in 17 percent of the women, but in only 2 percent of the men, the onset of psychosis occurred after age 35. The diagnosis of schizophrenia in these cases was made retrospectively according to *DSM–III* (American Psychiatric Association 1980) criteria. Goldstein et al. (1990), also used the *DSM–III* criteria, but without the criterion that limits the age at onset to 45 years, and found that the mean age at onset was 24.3 for men with schizophrenia and 27.9 for women with schizophrenia; 53 percent of the men and 32 percent of the women had become ill by the age of 25.

Applying the Research Diagnostic Criteria (Spitzer et al. 1978) to a Nigerian sample of schizophrenia patients, Gureje (1991) found that the mean age at onset of illness was 23.5 years for men and 26.4 years for women, with 83 percent of the male and 66 percent of the female patients becoming ill by age 30. He concluded that the gender difference in the age at onset of schizophrenia is present across cultures, implying a biological rather than a social etiology. However, in Gureje's study there was an uncertainty about some patients' birth years, and in some cases the data collection on the onset of illness was made by nonmedical personnel. In a better designed study of Nigerian schizophrenia patients, Ohaeri (1992) reported similar findings.

A later onset of schizophrenia for women has also been reported in a number of studies referring to patients with late-onset schizophrenia that is manifested after age 40 to 45 (Gold 1984; American Psychiatric Association 1987; Harris and Jeste 1988; Pearlson et al. 1989). Because most of these patients are female and show mainly paranoid symptomatology, the idea has been advanced that late-onset schizophrenia is a distinct entity (Gold 1984; Harris and Jeste 1988; Pearlson et al. 1989). Several of the studies on late-onset schizophrenia, however, are said to have methodologic problems, especially with the identification of cases and the applied diagnostic criteria (Harris and Jeste 1988).

Although the clinical subtypes of schizophrenic disorders comprise well-accepted nosologic entities (American Psychiatric Association 1987; McGlashan and Fenton 1991), the investigation of their relationship to the age at onset is inadequate. Gruenberg et al. (1985), in a study of reliability and concordance of the subtypes of schizophrenia according to four major diagnostic systems, showed that the age at onset for the paranoid subtype was significantly later than for the disorganized and the undifferentiated subtypes. Likewise, Fenton and McGlashan (1991), rediagnosing patients according to the subtype criteria, concluded that the paranoid subtype has a later age at onset, while the hebephrenic and the undifferentiated subtypes are early and insidious in onset.

Investigation of early schizophrenia, such as the study of first-admission patients, can provide clues for a better characterization of the disorder. Studying early cases allows the following: (1) minimization of the confounding effects of chronicity and institutionalization; (2) study of drug-free patients; (3) the opportunity to perform prospective longitudinal studies; (4) a greater likelihood of detecting factors related to the etiology or pathophysiology of the disease; and (5) increased understanding of the variability in clinical morbidity observed in the first few years of the onset of the disorder (Keshavan and Schooler 1992).

None of the previous investigations has attempted to study the five schizophrenic subtypes as separate entities (American Psychiatric Association 1987) taking into consideration both gender and age at onset. If, however, the schizophrenic subtypes have different etiologies, or are different expressions of the same basic defect, the subtypes can be expected to have, in addition to the known specific

clinical characteristics, differences in the age at onset as well as between the sexes. For this reason, we undertook to investigate the following: (1) the age at onset in the five subtypes of schizophrenic disorders, namely, the disorganized, catatonic, paranoid, undifferentiated, and residual; and (2) differences in the age at onset between male and female patients in each of these subtypes. Information in these areas could help reveal factors associated with the etiology of schizophrenia.

Method

We investigated the medical records of 163 successive hospital admissions of schizophrenia patients diagnosed from the beginning according to *DSM–III–R* criteria (American Psychiatric Association 1987). Among this group, 100 were male and 63 were female. Thereafter, only successive female cases were studied until the number of women patients grew to 100 and the total sample, males and females, was 200. All patients were hospitalized for the first time in the Department of Psychiatry of the University of Patras Medical School, Patras, Greece, from January 1988 through December 1992. Ninety-six of them were admitted for the first time in any psychiatric inpatient service; the remainder had one or more earlier hospitalizations elsewhere.

Patras is the third largest population center of Greece, located in the southwestern part of the country. The psychiatry department's wards are the only inpatient service in a larger administrative area of approximately 1 million people, and the department accepts cases with a 3-month maximum time of hospitalization.

The original diagnosis was made by staff psychiatrists during the patients' hospital stay after assessment of their history, clinical symptomatology, and overall behavior. To test reliability of the diagnosis, the records of each patient were reviewed independently by the three authors. The reviewers were blind to patients' age at onset of schizophrenia because this information was excluded from the case charts before assessment. For the present study, the diagnosis of the three reviewers was used. In all cases there was agreement by at least two of the reviewers. The unweighted kappa for interrater agreement among the three reviewers was 0.942 (z = 21.284, $p < 0.00001$). The interrater reliability among the three reviewers for the diagnosis of schizophrenia versus nonschizophrenia was estimated by reviewing 60 randomly selected case charts. There was complete agreement in all cases (kappa = 1.00, z = 6.213, $p < 0.00001$).

Three male patients, two with the paranoid subtype and one with the catatonic subtype, presented with the residual subtype on readmission. For the purposes of this study, they were given the later diagnosis of the residual subtype. Five additional cases of schizophrenic disorders (a male and a female with the paranoid subtype, two males with the residual subtype, and a male with the undifferentiated subtype) for whom the age at onset was uncertain were excluded from the study.

The onset of the disease was determined by the report of the immediate family and, when possible, by the patient specifying the time when the first prodromal symptoms required for a *DSM–III–R* diagnosis of a schizophrenic disorder were observed.

In addition to the unweighted kappa for three raters, Student's t test and the chi-square test were applied for the statistical analysis of the data. When multiple comparisons were made, the p value with the Bonferroni correction was estimated (Hochberg 1988). In general, p values smaller than 0.05 were considered significant.

Results

Table 1 shows the distribution of the 200 patients in the five subtypes of schizophrenic disorders and the age at onset in both males and females. The paranoid subtype was diagnosed most frequently in 39 of the males and 46 of the females.

The mean age at onset ± standard deviation (SD) of 30.4 ± 9.3 years observed in the paranoid subtype was the latest onset, whereas the 17.0 ± 2.2 years of the disorganized subtype was the earliest of all subtypes. The differences between the mean age at onset of the paranoid subtype and the mean age at onset of the other four subtypes were significant (disorganized: t = 12.45, df = 112, $p < 0.00001$; undifferentiated: t = 6.94, df = 133, $p < 0.00001$; residual: t = 5.77, df = 113, $p < 0.00001$; catatonic: t = 4.25, df = 89, $p < 0.001$). The mean age at onset of the disorganized subtype was significantly earlier than that of the residual subtype (t = 5.31, df = 57, $p < 0.00001$) or the undifferentiated subtype (t = 5.13, df = 77, $p < 0.00001$). There was no significant difference in the mean age at onset between the undifferentiated and the residual subtypes (t = 0.30, df = 78, $p > 0.05$); the disorganized and the catatonic subtypes (t = 1.86, df = 33, $p > 0.05$);

Table 1. Age at onset in schizophrenia patients according to subtype and sex (*n* = 200)

	Male		Female		Total	
		Onset		Onset		Onset
Subtype	*n*	mean (SD)	*n*	mean (SD)	*n*	mean (SD)
Paranoid	39	26.7 (6.7)	46	33.5 (10.1)	85	30.4 (9.3)
Undifferentiated	23	20.9 (3.7)	27	22.8 (5.3)	50	22.0 (4.7)
Residual	21	22.1 (4.6)	9	22.8 (6.8)	30	22.3 (5.2)
Disorganized	12	17.7 (1.6)	17	16.1 (2.4)	29	17.0 (2.2)
Catatonic	5	21.0 (5.5)	1	19.0 —	6	20.7 (5.0)
Total	100	23.0 (6.0)	100	26.6 (10.2)	200	24.8 (8.6)

Note—SD = standard deviation

the undifferentiated and the catatonic subtypes ($t = 0.61$, $df = 54$, $p > 0.05$); or the residual and the catatonic subtypes ($t = 0.74$, $df = 34$, $p > 0.05$) (Student's t test with Bonferroni correction).

The mean age at onset of all female patients was significantly later than that of male patients ($t = 2.95$, $df = 198$, $p = 0.017$). Further analysis of the age at onset showed significant differences between male and female patients within the subtypes of schizophrenic disorders.

In the paranoid subtype, the mean age at onset for females was significantly later than that for males ($t = 3.72$, $df = 83$, $p = 0.00017$). However, in the disorganized subtype, the disorder started significantly earlier in the female patients than in the male patients ($t = 2.20$, $df = 27$, $p = 0.018$). The mean onset of the undifferentiated subtype was earlier in the male than in the female patients, but the difference was not significant ($t = 1.89$, $df = 48$, $p = 0.07$). There was no significant difference in the mean age at onset between male and female patients of the residual subtype ($t = 0.25$, $df = 28$, $p = 0.40$).

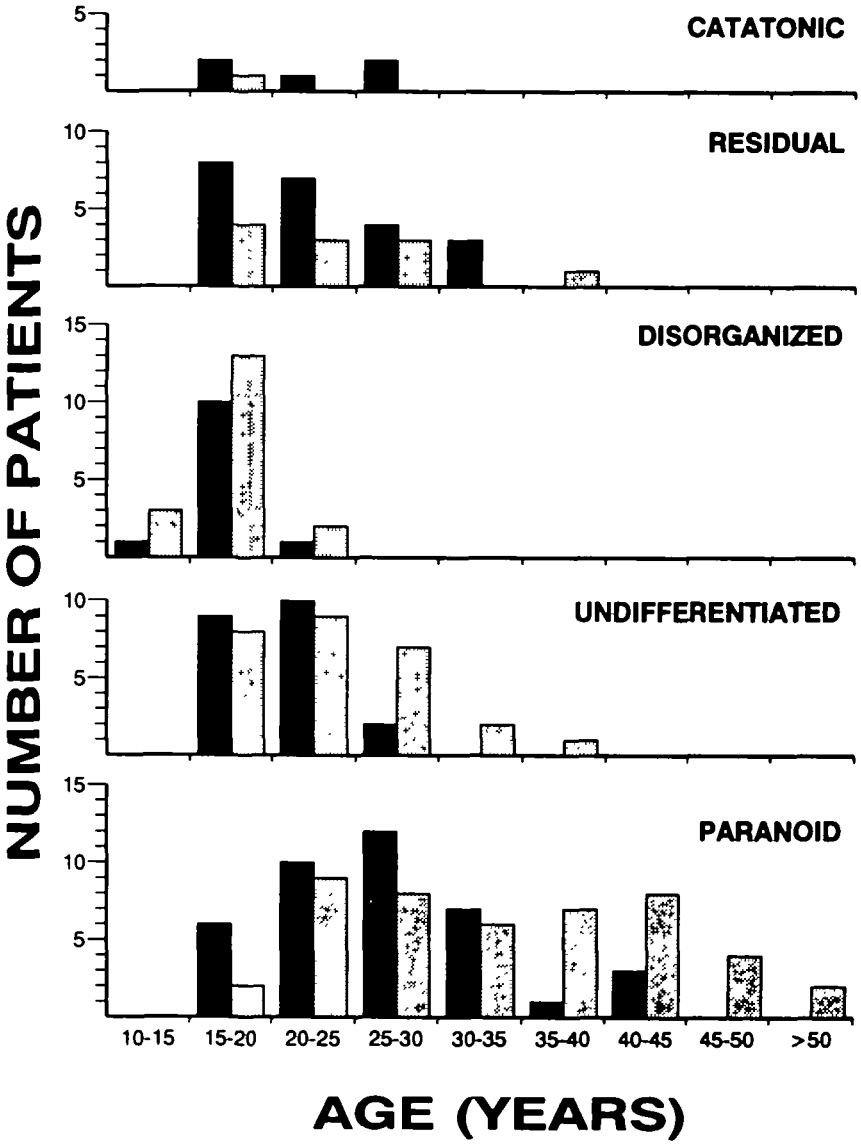
Table 2 lists the differences in the age at onset between the 39 male and the 46 female patients with the paranoid subtype. The number (28) of paranoid male patients with an age at onset before 30 was significantly greater than the 4 male patients who were diagnosed with the disorder after age 35 ($\chi^2 = 36$, $df = 1$, $p < 0.001$). On the contrary, there was no significant difference between the number of female subjects with age at onset before 30 (19 cases) and after 35 (21 cases) ($\chi^2 = 0.211$, $df = 1$, $p > 0.50$). Figure 1 illustrates the age at onset of the 200 patients in each of the five subtypes of schizophrenic disorders.

Of the 85 patients with paranoid subtype, approximately 72 percent of the male and 41 percent of the female patients showed the disorder before age 30. The onset occurred after age 35 in 10 percent of the male and 46 percent of the female cases. In the 30 to 35 age group, the onset occurred in 18 percent of the male and in 13 percent of the female cases (table 2). Analysis of the distribution of the age at onset of the 39 male and the 46 female subjects with the paranoid subtype showed that the percentage of males with an onset before age 30 was significantly greater than the percentage of females ($\chi^2 = 19.55$, $df = 1$, $p < 0.001$), whereas the percentage of

Table 2. Differences in age at onset between male and female paranoid patients (*n* = 85)

Age at onset (yrs)	Male (*n* = 39)	Female (*n* = 16)	Significance	
	n (%)	*n* (%)	χ^2	*p*
< 30	28 (72)	19 (41)	7.938	<0.01
30–35	7 (18)	6 (13)	0.392	>0.5
>35	4 (10)	21 (46)	12.737	<0.001

Figure 1. Distribution of age at onset of paranoid, undifferentiated, disorganized, residual, and catatonic subtypes of 200 schizophrenia patients (100 male and 100 female)



Solid bars = male; shaded bars = female.

females with onset after age 35 was significantly greater than that of males (χ^2 = 32.143, df = 1, p < 0.001). There was no significant difference between the percentage of the two sexes when the onset was between 30 and 35 years (χ^2 = 0.954, df = 1, p > 0.30).

The mean age at onset ± SD for the male patients with undifferentiated, residual, disorganized, and catatonic subtypes was 20.7 ± 4.1 years; for the female patients with the same subtypes it was 20.6 ± 5.7 years. This difference is not significant (t = 0.97, df = 113, p > 0.4). On the other hand, the mean age at onset ± SD (26.7 ± 6.7 years) of the male patients with the paranoid subtype was significantly greater than that of the female patients with all other subtypes of schizophrenic disorders (20.6 ± 6.7 years) (t = 4.54, df = 91, p < 0.0001).

When only first admissions were considered (n = 96; see table 3), analysis of the data confirmed the findings obtained from the total sample of the 200 patients. However, in this case no analysis could be made of the catatonic or residual subtypes because of the small number of such first admissions. The mean age at onset of first-admission paranoid patients to any hospital was 29.9 ± 9.4 years, whereas that of the first-admission patients with the undifferentiated subtype was 22.9 ± 5.3 years (t = 3.99, df = 69, p < 0.00001). There was also a significant difference in the age at onset between the first-admission patients with the paranoid and those with the disorganized subtype (16.7 ± 2.5 years; t = 8.75, df = 64, p < 0.00001). Similarly, in first-admission patients, the onset of the disease occurred significantly earlier in the disorganized than in the undifferentiated subtype (t = 5.13, df = 43, p < 0.00001) (Student's t test with Bonferroni correction).

Table 4 shows the differences in the age at onset between 22 male and 24 female first-admission paranoid patients. The number of the first-admission male paranoid pa-

Table 3. Age at onset in 96 first-admission schizophrenia patients according to gender and subtype

	Onset (yrs)					
	Male		Female		Significance	
Subtype	*n*	mean (SD)	*n*	mean (SD)	*t*	*p*
Paranoid	22	26.4 (6.4)	24	33.0 (10.8)	2.57	<0.007
Undifferentiated	9	22.6 (4.5)	16	23.1 (5.8)	0.24	>0.400
Disorganized	8	17.9 (1.8)	12	16.0 (2.6)	1.89	<0.037
Catatonic	2	26.5 —	1	19.0 —	—	—
Residual	1	19.0 —	1	15.0 —	—	—
Total	42	23.8 (6.2)	54	26.0 (10.6)	1.27	>0.100

Note.—SD = standard deviation.

tients with the age at onset before 30, was significantly greater than the male patients with onset of the disorder after age 35 ($\chi^2 = 18.427$, $df = 1$, $p < 0.001$). There was no difference in the number of the first-admission female patients with onset before age 30 or after age 35.

Discussion

These data demonstrate that there are not only sex differences in the age at onset of the schizophrenic disorders, but also differences in the mean age at onset among the various subtypes of schizophrenia. The subtype with the earliest appearance was the disorganized, for which the mean age at onset was approximately 5 years earlier than the undifferentiated and residual subtypes, and 13 years earlier than the paranoid subtype. The later appearance of the paranoid subtype was first recognized by Kraepelin (1919/1971).

In addition to the earliest onset, the disorganized subtype demonstrated the sharpest peak of incidence of the age at onset of all subtypes. For both men and women, all cases appeared in a 9-year span, between ages 11 and 20. The widest spread for age at onset was observed in the paranoid subtype, in which new cases appeared between 17 and 60 years of age. In this subtype, women had a much wider peak of incidence rates than men. For women the age at onset spread over a period of 42 years, whereas for men the spread was 26 years. Also, a wider peak of age at onset incidence rates was observed in women than in men with the undifferentiated subtype, except that the difference between the sexes was smaller (see figure 1). The small number of cases with the catatonic subtype does not permit meaningful comparisons of this subtype with the others.

Our observation that the mean age at onset in all subtypes of schizophrenic disorders we studied was 3.6 years earlier for men than for women is in accord with the findings of earlier reports (Noreik and Ødegaard 1967; McCabe 1975; Lewine 1980; Loranger 1984; Goldstein et al. 1990; Gureje 1991). This sex difference has been demonstrated regardless of the historical period, culture or diagnostic system applied (Bleuler 1911/1950); Kraepelin 1919/1971; Lewine 1981; Loranger 1984; Goldstein et al. 1990; Gureje 1991).

The significantly earlier onset of schizophrenia in female patients with four of the five subtypes (disorganized, undifferentiated, residual, catatonic) when compared with male patients with the paranoid subtype demonstrates that men do not always have an earlier age at onset of the schizophrenic disorders than women and indicates the existence of differences among the subtypes of schizophrenia. Furthermore, this finding helps to explain the observation that age distributions of the two sexes do not consist of two isomorphic curves separated by a time interval (Loranger 1984), for there are female patients with an early onset as well. The existence of differences in the age at onset

Table 4. Differences in age at onset between first-admission male and female paranoid patients

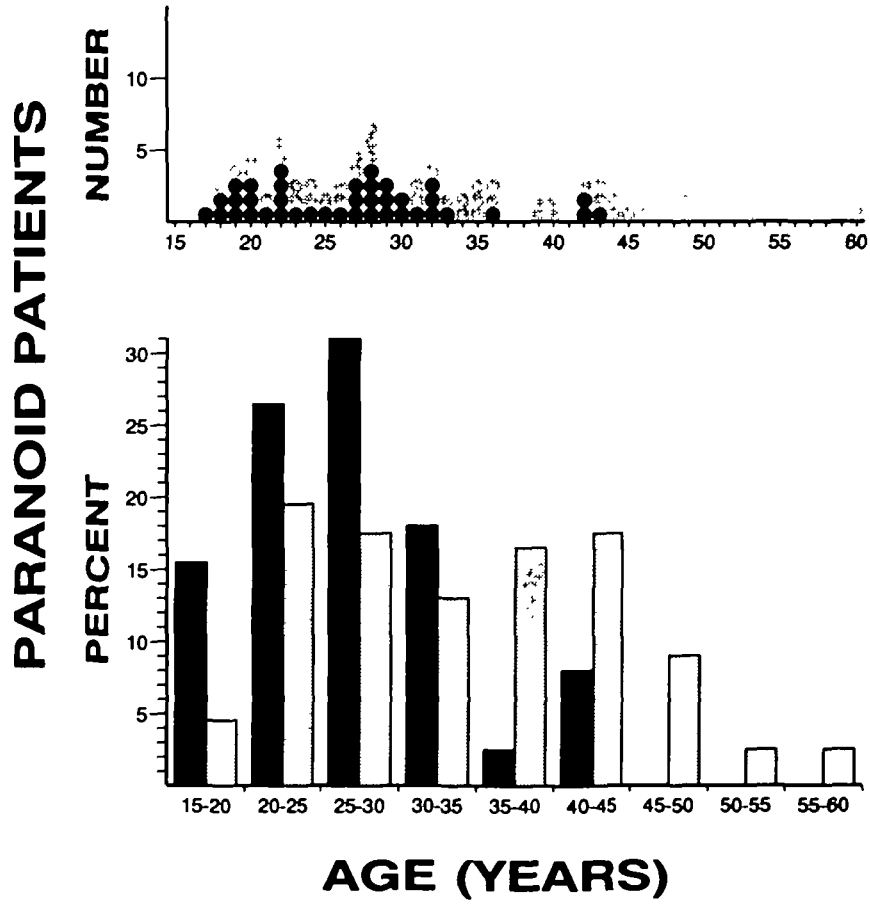
Age at onset (yrs)	Male (*n* = 22)	Female (*n* = 24)	Significance	
	n (%)	*n* (%)	χ^2	*p*
<30	16 (73)	10 (42)	5.64	<0.02
30–35	4 (18)	3 (12)	0.29	>0.50
>35	2 (9)	11 (46)	7.64	<0.01

among the subtypes of schizophrenic disorders is also evidenced by the fact that the mean age at onset between all male and female cases in the present study was significantly greater in the female cases, whereas male and female cases of all other subtypes, except the paranoid, had an almost identical mean age at onset, differing only by a factor of 0.1 years.

The findings of the study indicate that the overall earlier onset of schizophrenia in men is caused by the impact of the significantly earlier onset of the disorder in men of the paranoid subtype. This observation does not support the hypothesis that estrogens or androgens, either as fetal hormones affecting the structure and functioning of the brain (organizational effects) or as circulating hormones (triggering effects), cause the gender differences in the age at onset of schizophrenia (Seeman 1985; Seeman and Lang 1990). If estrogens play a protective role or androgens a triggering role in the age at onset, this should be limited to the paranoid and, possibly, the undifferentiated subtypes. However, such a selective effect of these hormones is plausible only if the subtypes are the phenotypic expression of biological or genetic heterogeneity of schizophrenia.

The observation that 72 percent of the men with the paranoid subtype became ill before age 30, whereas only 10 percent developed the illness after age 35, demonstrates the tendency of men to develop the paranoid subtype of schizophrenia before the age of 30; the peak period of onset is between ages 25 and 29. On the contrary, the finding that women show a similar age at onset distribution before their 30th birthday (41%) and after their 35th (46%) leads to the conclusion that women have an equal risk for developing the disorder earlier or later in life. Actually, women appeared to have two peaks in the age at onset, one from ages 20 to 24, and the other from ages 40 to 44. It is of interest that even men showed a small increase in the frequency of the age at onset from ages 40 through 44. The lowest frequency of the age at onset in the age span of 20 to 45 years was found from ages 30 through 34. After age 45 the frequency of the onset of the disorder starts decreasing, with the latest onset observed at age 60 (see figure 2). These observations may indicate the presence of two peaks in the age at onset, suggesting the existence of two different forms of the disorder. This possibility is supported by the finding that patients

Figure 2. Age at onset for 85 schizophrenia patients, paranoid subtype



Vertical bars = percentage of age at onset in each sex per 5-year period. Dots = distribution of age at onset of 85 patients Solid symbols = male; shaded symbols = female. Each dot corresponds to one individual.

with paranoid schizophrenia had a greater stability of the subtype when the onset occurred after age 30 (Kendler et al. 1985). Further investigation of this aspect is warranted.

The differences in the age at onset among the subtypes of schizophrenic disorders observed in this study appear to be real, as they are highly unlikely to have resulted from the selection criteria used for the admission of patients. If such a factor had operated, a similar trend should exist in all subtypes. The patients included in the study were unselected, with the exception of the successive female patients only selected after 100 male cases were obtained. Only 5 cases were excluded, because their age at onset was uncertain.

The fact that the 96 schizophrenia patients admitted for the first time to any hospital demonstrated findings similar to those in the total sample of 200 patients supports the position that the study data reflect the real phenotypic expression of the subtypes and do not result from the confounding effects of chronicity, drug treatment, or institutionalization.

Also, since the number of studies examining first-episode schizophrenia is relatively small (Keshavan and Schooler 1992), the data on the first hospitalization sample can be used for comparisons with the multiple-episode cases.

The earlier onset of the disorganized subtype in the female when compared with the male patients should be looked at as representing one extreme of the spectrum of the gender differences in the age at onset among the subtypes of the schizophrenic disorders. The paranoid subtype has an earlier onset of 6.8 years in the male patients, followed by an earlier onset of 1.9 years in the undifferentiated subtype (again in the male patients), a nonsignificant difference between the sexes of 0.7 years for the residual subtype and an earlier onset by 1.6 years in the female patients for the disorganized subtype. This gradual transition of the age at onset between the sexes in the subtypes, observed in both the multiple and first-admission patients, suggests that it does not result from a cultural ascertainment bias, but rather that it is an intrinsic characteristic of the subtypes.

Age at onset is an important clinical finding of schizophrenia that could be helpful in shedding light on the primary defect of the disorder. The findings of this study provide evidence of both gender and subtype differences in the age at onset of the schizophrenic disorders and may help to clarify the clinical spectrum and etiology of the subtypes.

The division of schizophrenia into subtypes has been controversial, and Blashfield (1973) claimed that the subtypes cannot be reliably diagnosed. However, more recent studies have demonstrated adequate to excellent reliability of the subtyping of schizophrenia (Gruenberg et al. 1985). In a review article, McGlashan and Fenton (1991) addressed the question of whether or not there is a reason to maintain the subtypes of schizophrenia in *DSM–IV* and concluded that all of them should be retained. The data presented in this article provide additional support for the validity of the schizophrenic subtypes as distinct clinical entities.

It has been suggested (DeLisi et al. 1987; Crow 1988) that one of the genes of schizophrenia, perhaps that which determines time of onset, could be sex linked. This hypothesis, however, seems unlikely for the entire group of schizophrenic disorders in light of the findings of the present study showing both variable gender differences and differences in the age at onset among the subtypes regardless of sex.

A genetic predisposition for schizophrenia is widely accepted, but segregation analyses of pedigrees have failed to identify a classic single gene pattern of inheritance. However, the variable clinical picture of the disorder could be attributed to underlying genetic heterogeneity. When we are considering a disease, we need to be sure that we are talking about the same entity. In genetic heterogeneity the same clinical picture can be caused by more than one mutation at different loci. On the other hand, pleiotropism, the multiple effects of a single mutant gene, can lead to different phenotypes. The question, therefore, as to whether or not all or some of the subtypes of the schizophrenic disorders are the result of genetic heterogeneity or pleiotropism remains unsettled.

In seeking to better understand the etiology of schizophrenic disorders one can rely on clinical, genetic, and biochemical data. Biochemical evidence is the most reliable category of evidence. Although the biological basis of schizophrenia remains unknown, it seems that genetic studies may provide clues to the primary defect of the disorder.

The differences in the age at onset of the schizophrenic disorders we described may indicate biological differences among the subtypes or groups of subtypes. If these differences had an environmental origin, such as social pres-

sures, we would expect to find a similar trend in the age at onset of the two sexes among the subtypes. Therefore, genetic studies, which will take into consideration the phenotype of the schizophrenic disorders, are needed. If such studies can provide evidence of genetic heterogeneity, phenotypic differences will attain their proper perspective, and earlier unnoticed differences, similar to those reported in this article, may emerge to serve as truly diagnostic phenotypic features.

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Providing a forum for a lively exchange of ideas ranks high among the *Schizophrenia Bulletin's* objectives. In the section **At Issue,** readers are asked to comment on specific controversial subjects that merit wide discussion. But remarks need not be confined to the issues we have identified. **At Issue** is open to any schizophrenia-related topic that needs airing. It is a place for readers to discuss articles that appear in the *Bulletin* or elsewhere in the professional literature, to report informally on experiences in the clinic, laboratory, or commmunity, and to share ideas—including those that might seem to be radical notions. We welcome all comments.—*The Editors.*

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