The Epidemiology of Late-Onset Schizophrenia

by David J. Castle and Robin M. Murray

Abstract

We report an analysis of a large catchment area sample of patients with nonaffective functional psychoses presenting across all ages at onset. The male:female ratio was 1.56:1 in the 16–25-year age group; it reached unity around 30 years of age and declined to 0.38:1 in the 66–75-year group. Contrary to expectation, a higher proportion of patients with onset of illness after 45 years than of younger onset patients fulfilled *DSM–III–R* criteria for schizophrenia (52% vs. 38%). The distribution by age at onset was much the same irrespective of stringency of diagnosis. The highest rates were in the 16–25-year age group, with a slight second peak in the 46–55-year group, and a third (more emphatic) peak in the over-65 group. A closer analysis of demographic and phenomenologic variables revealed distinct differences between patients with early and late (after 44 years) onset of illness.

Despite the plethora of epidemiologic investigations of schizophrenia, late-onset illness has all too often been ignored. This lack of interest (until recently) in late-onset schizophrenia is due, at least in part, to the tacit acceptance (particularly in the United States) that schizophrenia cannot manifest for the first time after 44 years of age. This view is embodied in the *DSM–III* criteria for schizophrenia (American Psychiatric Association 1980). The European tradition has been somewhat different, and ICD–9 (World Health Organization 1978) does not have an age-of-onset stipulation for schizophrenia; furthermore, paraphrenia, akin to Roth's (1955) concept of "late paraphrenia" as a paranoid delusional illness with onset usually after the age of 60, is recognized in ICD–9, although it has been dropped from drafts of ICD–10.

It is thus not surprising that most of the published investigations of the epidemiology of late-onset schizophrenia are to be found in the European literature. The bulk of the studies have been of the prevalence of late-onset schizophrenia in hospitalized samples. Fewer investigators have tried to assess the prevalence in community samples, and there have been even fewer incidence studies specifically of late-onset illness. An excess of females among late-onset schizophrenia patients has been widely reported, but few studies have addressed this matter directly. We have conducted an incidence study of schizophrenia and related conditions across all ages at onset, using a first-contact catchment area sample (see Castle et al. 1991, 1993*b*; Wessely et al. 1991). This article focuses on patients with an onset of illness after the age of 44 years and pays special attention to gender differences. First, we supply a brief overview of the relevant literature.

Literature Review

Studies of the prevalence and age-at-onset distribution of late-onset schizophrenia have recently been reviewed by Harris and Jeste (1988). They noted a marked inconsistency in the reported find-

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ings, due in part to differences in case-finding methodology and a failure to employ standardized diagnostic criteria. On the basis of eight studies that reported the occurrence of late-onset schizophrenia among schizophrenia patients of varying ages, Harris and Jeste estimated (weighted means based on sample size) that around 23 percent of schizophrenia patients could be considered to have a late onset of illness (generally onset after 40 years); the range was 15.4 to 32.0 percent. The mean proportion of late-onset schizophrenia patients in populations of elderly patients with schizophrenia was 31 percent.

Ten of the studies reviewed by Harris and Jeste (1988) reported on differences in the proportions of schizophrenia patients with age at onset before and after age 60 years. The weighted means showed that around 14 percent of late-onset (usually after 40 years) schizophrenia patients first manifested the illness after age 60. Six of the studies gave a further breakdown of age at onset. A mean of 57.5 percent of the late-onset patients had an onset between 40 and 50 years, 30.2 percent between 50 and 60 years, and 12.3 percent after 60 years. These figures translate to around 13 percent (40–50 years), 7 percent (50–60 years) and 3 percent (after 60 years) of all schizophrenia patients.

It is important to note that almost all of the studies reviewed by Harris and Jeste (1988) were based on unselected samples of patients, and thus were not true prevalence studies. Also, most were based on patients admitted to a hospital. There have been very few studies of the community prevalence of late-onset schizophrenia. Post (1966) outlined the difficulties inherent in such studies. Post pointed to the fact that Kay et al. (1964), in a community study, identified no patients fulfilling Roth's (1955) criteria for late paraphrenia among 309 persons over 65 years of age in Newcastle, England, although it was later found that at least 8 patients from that population had been hospitalized or institutionalized with late paraphrenia. In community surveys, Parsons (1964) found a prevalence of late paraphrenia of 1.7 percent among persons over 65 in a Welsh town, and Williamson et al. (1964) found a prevalence of 1 percent in a Scottish borough. More recently, Christenson and Blazer (1984) found that 4 percent of 997 elderly persons exhibited symptoms of pervasive persecutory delusions. From a five-site epidemiologic catchment area (ECA) study in the United States, Keith et al. (1991) reported 1-year prevalence rates for schizophrenia of 0.6 percent for 45–64-year-olds, falling to 0.2 percent among those over 65. The rate for 18–29-year-olds was 1.2 percent, and for those aged 30–44, 1.5 percent. Because the ECA figures are based solely on self-report by the interviewed subjects, they must be viewed with some caution.

An alternative approach, which avoided diagnostic issues, was used by Tien (1991), who established incidence rates for hallucinations, by age and sex, in the ECA study. Between the ages of 18 and 60, the incidence of visual hallucinations was slightly higher in males than in females, but after age 60 (and particularly after age 80) there was an emphatic rise in the rates for females. For males, there was a much more modest rise at around 70 years of age. Auditory hallucinations showed a different distribution, with a peak for males at 25–30 years; females showed a later peak at 40–50 years, with a subsequent rise after 70. Of course, hallucinations are not pathognomonic for schizophrenia, but they are often manifestations of the illness. Thus, these data provide an insight into sex effects in the aging brain, and they have implications for our understanding of age and sex effects in schizophrenia itself.

Few investigators have specifically assessed the incidence of late-onset schizophrenia. Kay (1972), using first-admission data from England and Wales for 1966, found rates of schizophrenic illnesses (including paranoia and paranoid states) in persons over 65 years of age to be between 10 and 15 per 100,000 for males and between 20 and 25 per 100,000 for females.

Of course, incidence rates determined from hospital admission data are necessarily biased and almost certainly underestimate the true incidence of the disease. Even though there have been claims that practically all schizophrenia patients are eventually admitted to a hospital, the available data do not support this assumption. For example, we (Castle et al., in press) found that 20 percent of a catchment area sample of patients with nonaffective functional psychoses were not admitted at first psychiatric contact, whereas Geddes and Kendell (1992) reported that 8 percent of schizophrenia patients on the Lothian Psychiatric Case Register in Scotland had never been admitted to a psychiatric hospital. In the ECA study, a massive 40 percent of patients who received a lifetime diagnosis of schizophrenia reported that they had never had a psychi-

atric admission (Keith et al. 1991). There are reasons to suspect that late-onset schizophrenia patients are particularly unlikely to be admitted. Such individuals often have a long history of eccentricity and social isolation, yet they are not usually educationally or occupationally compromised (e.g., Kay and Roth 1961; Post 1966). Thus, many individuals in this group might be able to continue to function in the community even when deluded; their lack of friends and other social contacts would militate against such individuals' coming to the notice of the psychiatric services. Indeed, in the survey of community elderly by Christenson and Blazer (1984) quoted above, only half of the individuals exhibiting pervasive persecutory delusions perceived the need for help, and very few had had psychiatric contact.

One way in which some of the bias arising from the use of hospitalized patient populations can be avoided is by the use of psychiatric case registers, which record all contacts with psychiatric services, not just admissions. We are aware of only one study that has employed such a register specifically to examine the incidence of late-onset schizophrenia. In this study, Holden (1987) estimated annual rates of late paraphrenia of 17 to 24 per 100,000 population, depending on whether "organic" cases were included; one problem with the study is the very small sample size and the resulting wide confidence limits.

Gender differences in late-onset schizophrenia have been widely reported. Indeed, an excess of females has been seen in almost all studies that have included both sexes. The male:female ratio in the over-40 group ranges from 3:5 (Bland 1977) to 1:1.9 (Bleuler 1943/1972); in very-late-onset cases (onset after 60), the preponderance of females is even more marked, ranging from 1:3 (Roth 1955) to 2:45 (Herbert and Jacobsen 1967). Figure 1 shows first-admission rates for schizophrenia, by sex, for England in 1984. It will be noted that there is a dramatic excess of males under age 40, while females predominate in the later onset patients. The male:female ratio peaks at 2.1:1 in the 20–24-year age group, reaches unity at around the age of 40, and declines to 0.6:1 at around 65 years.

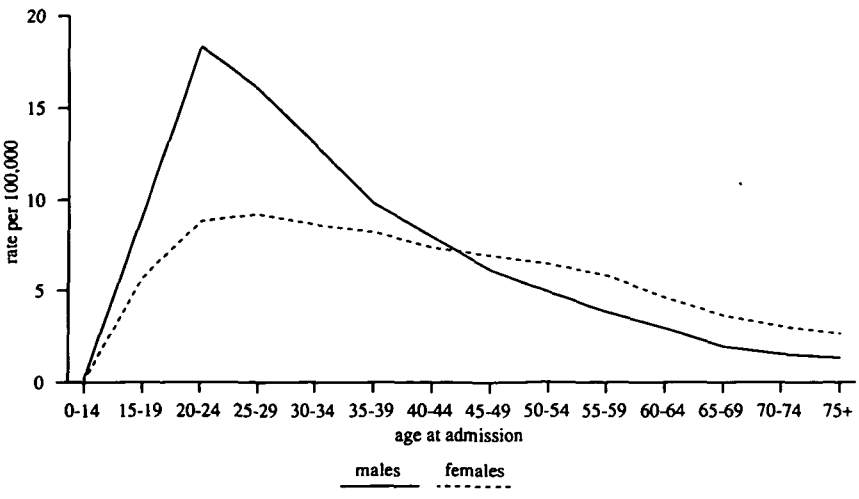
The large study of Bland (1977) suggested an increase in the female:male ratio with increasing age at first hospitalization, but the data presented in figure 1 are equivocal in this respect. Again, one of the difficulties with these studies is that they are based almost exclusively on hospitalized samples, leading investigators to draw conclusions on the basis of relatively severely affected patients.

The Camberwell Study

Patients, Materials, and Methods. The patients, ascertained through the Camberwell Cumulative Psychiatric Case Register (Wing and Hailey 1972), were all nonaffective, nonorganic psychotic individuals from the Camberwell catchment area who had their first contact with psychiatric services between 1965 and 1984. Thus, not only inpatients but also those seen as outpatients or on domiciliary visits were included. The Camberwell catchment area is a deprived inner-city area in Southeast London, England, that rates high on deprivation indices that are based on such factors as housing tenure and socioeconomic status (see Balarajan et al. 1992).

The study was conducted over a 20-year period, during which the demography of the area changed considerably. The total population declined from 171,000 in 1965 to 118,000 in 1984. In contrast, there has been an influx into the area of

Figure 1. First-admission rates for schizophrenia per 100,000 population, by sex (England, 1984)



persons born in the Caribbean; the proportion of such persons in the general population rose from 2.5 percent in the 1961 census to 6.6 percent in the 1981 census. Because these individuals came to the United Kingdom in their early adulthood and have subsequently produced children here, Afro-Caribbeans in Camberwell are generally younger than their (United Kingdom-born) Caucasian counterparts. Thus, it is not surprising that in our schizophrenia sample, the mean age of onset was lower for Afro-Caribbeans (28.3 years for males, 31.2 years for females) than for Caucasians (33.7 years for males, 46.2 years for females). Overall, however, there has been remarkably little change in the age structure of the population in the years under study. In 1965, 38 percent of males and 35 percent of females were under 25, and 66 percent of males and 61 percent of females were under 45. The comparable figures for 1984 were 37 percent of males and 35 percent of females under 25, and 65 percent of males and 61 percent of females under 45. The male:female ratio also remained stable over the years. (The population was 48 percent male in both 1965 and 1984.)

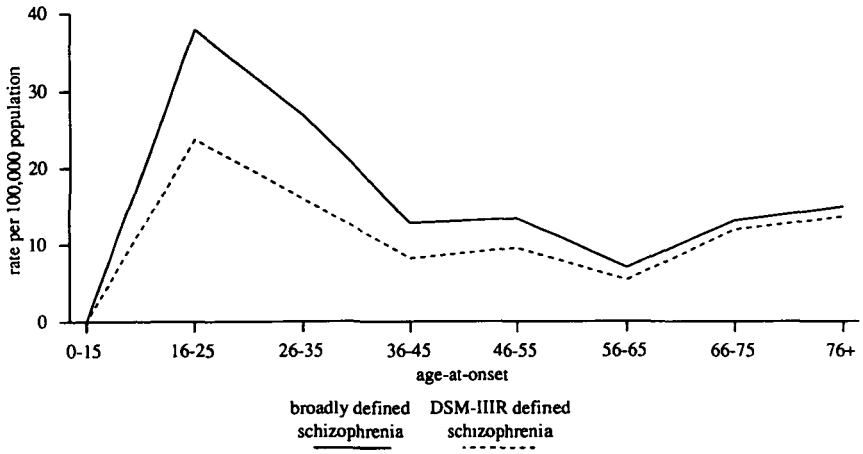
In the present study, the broadest feasible range of diagnoses was reviewed: schizophrenia (ICD–9 codes 295.0–295.9), including schizoaffective type (ICD–9 295.7); paraphrenia (ICD–9 297.2); and "other nonorganic psychoses" (ICD–9 298.1–298.9). This range was selected to avoid bias from preselection according to any single set of diagnostic criteria and to ensure inclusion of patients with any age at onset. Case charts of each individual were obtained and all medical, nursing, social work, and occupational therapy notes were examined. Most patients were seen by the psychiatric services of the Maudsley, Bethlem Royal, and Kings' College Hospitals, where the quality of the written charts is high; in most cases, a comprehensive semistandardized case summary was also available (Institute of Psychiatry 1973). Patients who had had psychiatric contact before 1965 were excluded from further analyses, as were patients whose illness had an obvious organic basis. The Operational Criteria Checklist for Psychotic Illness (OCCPI; McGuffin et al. 1991), which provides a simple and reliable way of applying operational diagnostic criteria in studies of psychotic illness, was completed for each individual. Diagnoses were computed with the computer program OPCRIT (McGuffin et al. 1991). Two independent workers rated the charts; interrater reliabilities for diagnosis, determined on a random sample of 50 charts rated by both workers, were good (kappa = 0.82 for Research Diagnostic Criteria [Spitzer et al. 1978] diagnoses and 0.74 for *DSM–III–R* [American Psychiatric Association 1987] diagnoses). Age at onset, defined as "the earliest age at which medical advice was sought for psychiatric reasons or at which symptoms began to cause subjective distress or impair functioning" (as in OCCPI), showed excellent interrater reliability (kappa = 0.93, performed by 5-year age-at-onset bands).

Demographic figures for the Camberwell catchment area were determined by interpolating Office of Population Censuses and Surveys data from the 1961, 1971, and 1981 censuses (100% samples).

Results. A total of 470 patients' case charts were rated. The records of another 55 patients (10% of the total) had been lost or destroyed owing to lack of storage space at one of the local hospitals. There is no reason to suspect any systematic bias arising from the missing charts; the sex and age-at-contact distributions and register diagnoses did not differ significantly between the patients for whom charts were found and those for whom they were missing. Because the Register did not record whether patients were actually admitted at first contact, we cannot comment on whether patients for whom charts were lost differed from the rest in this respect, but any such bias would have very little impact on our results.

Incidence rates. Figure 2 shows annual incidence rates for broadly defined schizophrenia and related disorders, as well as for those individuals fulfilling *DSM–III–R* criteria for schizophrenia. The appropriate proportions of patients in the total sample fulfilling *DSM–III–R* criteria in each 10-year age-at-onset band were used to adjust the *DSM–III–R* rates for missing charts. Contrary to expectation, a higher proportion of patients with onset of illness after 44 years than of younger onset patients fulfilled *DSM–III–R* criteria for schizophrenia (52% vs. 38%). This age effect is underlined by the fact that later onset patients were also more likely to have had an illness lasting more than 6 months (53% of those over 44 vs. 36% of patients with onset before 45 years). The distribution by age at onset was much the same irrespective of stringency of diagnosis. The highest rates were in the 16–25-year age group, with a slight second peak in the 46–55-year

Figure 2. First-contact rates per 100,000 population, for broadly defined and *DSM–III–R*–defined schizophrenia (Camberwell, SE London)



DSM–III–R (American Psychiatric Association 1987).

group, and a third (more emphatic) peak in the over-65 group.

Phenomenological and demographic issues. The data on diagnostic criteria are somewhat misleading, in that a closer analysis of phenomenological variables (see Howard et al., in press) revealed distinct differences between patients with early and late (after 44 years) onsets of illness (all ratings as detailed in OCCPI). Specifically, formal thought disorder, passivity phenomena, thought interference, and negative symptoms (paucity of thought or speech, restricted affect) were more common in patients with an onset of illness before 45 years of age, whereas persecutory delusions, particularly those in an elaborately organized form, and all forms of auditory hallucination were more common in the late-onset group.

In terms of premorbid parameters, patients with an onset of illness after 45 years of age fared better than their early-onset counterparts. Comparisons of the two groups on levels of educational achievement were not meaningful because opportunities and expectations regarding schooling and tertiary education have changed markedly in the latter half of this century, a situation underlined by the fact that fully 84 percent of our later onset group had not had any education after age 14. However, OCCPI criteria for premorbid work adjustment are not prejudiced by educational achievement, and the early- and late-onset groups differed markedly in this regard; 50 percent of the former but only 15 percent of the latter were judged to have had poor premorbid work adjustment (χ^2 = 49.9, df = 1, $p < 0.0001$). Similarly, 22 percent of late-onset versus 43 percent of early-onset patients were rated (by OCCPI criteria) as having shown poor premorbid social adjustment (χ^2 = 19.2, df = 1, $p < 0.0001$). Consonant with this finding, 66 percent of the later onset group were or had been married; the proportion in the early-onset group was only 33 percent (χ^2 = 41.7, df = 1, $p < 0.0001$).

Gender differences. The mean age of onset of illness for the broadly defined schizophrenia group was 31.2 years for males and 41.1 years for females. Figure 3 shows the proportion of males and females in each 10-year age-at-onset band. Nearly half of the male patients had an onset of illness before the age of 25 years; thereafter there was a monotonous decline. Only 12 percent of male patients first manifested their illness between the ages of 46 and 65, and 4 percent after 65 years of age. In contrast, less than a third of the females had manifested their illness by the age of 25, and the overall age-at-onset distribution for females was more even over the years; 20 percent had an onset of illness between the ages of 46 and 65 years, and fully 18 percent had onset after the age of 65.

The dramatic differences between the sexes in age-at-onset distribution is also seen in figure 4, which shows male:female ratios by 10-year age-of-onset bands. The ratio is greater than 1:1 under the age of 35, after which the ratio declines dramatically to 3:20 in the group over age 75.

Discussion. This study has the advantage of being based on a first-contact sample, thus precluding bias related to hospitalization policies. We consider that the sample is a reasonably accurate reflection of schizophrenia in Camberwell, inasmuch as most schizophrenia patients in the United Kingdom have contact with

Figure 3. Percentages of male and female schizophrenia patients, by age at onset

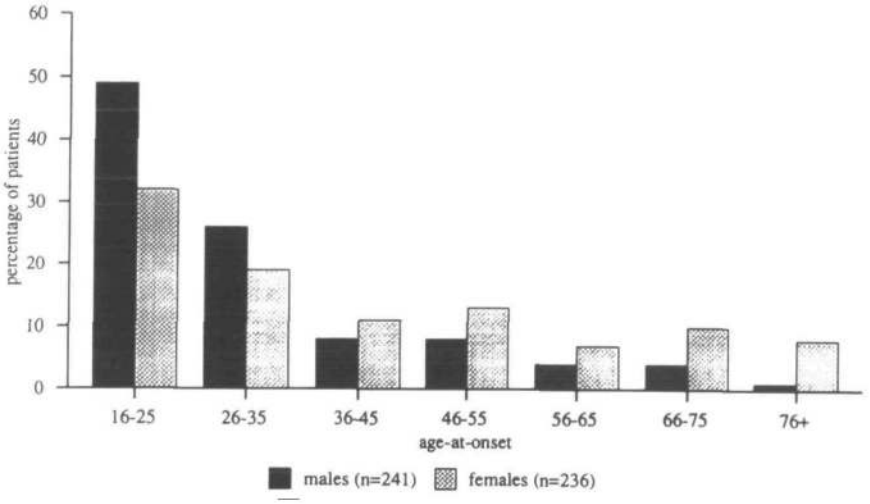
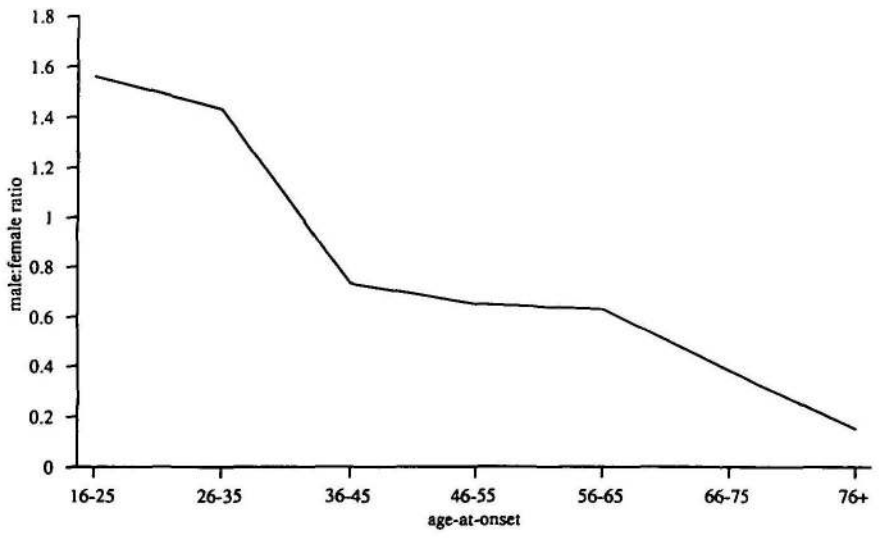


Figure 4. Male:female ratio of schizophrenia patients, by age at onset



the psychiatric services within 2 years of onset of illness (Cooper et al. 1987). However, as discussed above, there are reasons to suspect that persons with onset of a paranoid psychosis in later life are less likely to make contact with the psychiatric services, and this possibility must be considered in interpreting our data. What is of interest is that in the present sample, similar proportions of early- and late-onset patients were actually admitted to hospital at first psychiatric contact (78% of those with onset before 45 years, and 80% with onset after 44).

A particular strength of our study is the fact that we included the widest feasible range of patients, across all ages at onset, to avoid drawing conclusions on the basis of a sample preselected according to a specific set of diagnostic criteria.

Incidence and diagnosis. Twenty-eight percent of the patients in our sample had an onset of illness after age 44, and 12 percent after age 64. These figures are somewhat higher than the proportions estimated by Harris and Jeste (1988). Of interest is the high proportion of late-onset patients who fulfilled stringent *DSM–III–R* criteria for schizophrenia. Few other studies have reported on how many late-onset schizophrenia patients meet operationalized criteria for schizophrenia, but Rabins et al. (1984) found that 21 of 35 (60%) of their group of patients with onset after 44 years met *DSM–III* criteria for schizophrenia after the age-at-onset stipulation was removed. Thus, the manifestation of stringently defined schizophrenia is by no means confined to younger ages. The incidence curves for schizophrenia in our sample underline this fact. Even when only those patients fulfilling *DSM–III–R* criteria are considered, the annual incidence rate for late-onset schizophrenia was 12.6 per 100,000 population, half that for the 16–25-year age group.

The phenomenologic differences we found between early- and late-onset patients are largely in keeping with previous reports. For example, in a comparative case-note study, Pearlson et al. (1989) found that, compared with their early-onset counterparts, schizophrenia

patients with an onset of illness after the age of 44 were more likely to be deluded and to experience hallucinations; in contrast, they were much less likely to exhibit formal thought disorder or affective blunting. Such findings suggest that it is premature to consider early- and late-onset schizophrenia patients homogeneous, and there are implications for our understanding of the etiology of this group of conditions. These implications are discussed in further detail below.

The fact that late-onset patients were more likely than early-onset patients to have shown good premorbid adjustment in occupational terms is also consonant with the literature (e.g., Post 1966). Previous investigators (e.g., Kay and Roth 1961; Post 1966) have noted that many very-late-onset schizophrenia patients have been somewhat socially isolated throughout their lives. Our finding that those in the early-onset group were particularly likely to have exhibited poor premorbid social adjustment, places such reports in context and underscores data from many sources (see Murray et al. 1992 for a review) that early-onset schizophrenia patients have a pernicious form of the illness that is particularly likely to be associated with premorbid dysfunction (see below). The higher marriage rates in the later onset patients could be interpreted in the same way, although of course they may merely reflect the later onset of illness in that group.

Gender differences. A later onset of schizophrenia in females is a remarkably consistent finding across studies; the difference is usually on the order of 5 years (see Lewine 1988). Most studies examining this question have confined themselves to younger patients; certainly few have included those with an onset after the age of 60. The wide sex differential in age at onset in our study is due to the inclusion of the late- and very-late-onset groups, among which there is a marked preponderance of females.

One explanation for the sex difference in age at onset is that some factor or factors serve to delay the onset of schizophrenia in women. The distribution of patients in the current sample does not lend itself to this interpretation, in that the distributions (see figure 3) are so different for males and females and are not merely shifted to the right for women. It is possible that a number of factors, affecting men and women differentially, precipitate the first episode of schizophrenia at various ages. For example, it has been suggested that androgens may precipitate psychosis in adolescent males (see Seeman 1985). Conversely, it has been proposed that in the reproductive-age groups, women are somehow "protected" by the antidopaminergic effect of estrogens, and the slight peak in females in the 46–55-year age range is a result of the removal of such protection at menopause (Häfner et al. 1991). However, such a theory cannot explain the massive gender difference in very-late-onset patients. The fact that men appear to lose dopamine D_2 receptors at a faster rate than women (Wong et al. 1984) may be relevant here, but this remains highly speculative.

We favor the interpretation that men and women are differentially prone to subtypes of schizophrenia. We have argued elsewhere (Castle and Murray 1991; Murray et al. 1992) that early-onset schizophrenia, in which males predominate, is a consequence of neurodevelopmental deviance. We have also suggested, on the basis of phenomenologic and family history data, that some later onset females have a form of illness with etiological links to affective disorder. In a latent-class analysis of the current data set, we (Castle et al. 1992) defined three types of illness: (1) a "neurodevelopmental" form (type A), with a preponderance of males; (2) a "paranoid" form (type B), with a roughly equal male:female ratio; and (3) a "schizoaffective" form (type C), almost exclusive to females. Almost all of the patients in the neurodevelopmental group (type A) manifested their illness for the first time before the age of 30 years, whereas the age-at-onset distribution for the other two forms was more even over the years. In etiological terms, type A patients showed strong loading for family history of schizophrenia and for those obstetric complications that have been implicated in the etiology of neurodevelopmental schizophrenia (see Lewis and Murray 1987).

In contrast, type C patients had negligible family risk for schizophrenia but a high risk for other psychiatric disorders (mostly affective disorder); this finding supports the assumption that some late-onset schizophrenia patients have a disorder with etiological links to affective disorder. An intriguing finding was that type B schizophrenia was associated with winter birth, implying that some seasonal environmental factor (possibly a virus; see Sham et al. 1992) may be important in this group of patients. Of course, this typology requires replication in an independent sample, but it serves as

an example of approaches to unraveling the etiologies of schizophrenia of any age of onset. One caveat: the typology does not adequately explain patients with a very late onset of illness ("late paraphrenia"). Recent findings (reviewed by Castle and Howard 1992) that a substantial proportion of such patients have structural brain abnormalities and mild cognitive deficits (Holden 1987; Hymas et al. 1989) suggest that organic brain dysfunction serves as a "final common pathway" in many patients in this group (Murray et al. 1992).

Conclusions

In this article we have concentrated on incidence rates and sex differences in late-onset schizophrenia. We chose to examine this area largely because there is very little published information about epidemiologic issues in patients with a late onset of illness. Current issues that are the subject of heated debate in the literature have simply not been addressed in late-onset patients. For example, (1) Is the incidence of schizophrenia declining in Western countries? (See Crow 1990; Der et al. 1990; Prince and Phelan 1990; Häfner and Gattaz 1991.) (2) Is exposure to an influenza virus in utero an etiological factor in schizophrenia? (See Mednick et al. 1988; Kendell and Kemp 1989; Crow et al. 1991; O'Callaghan et al. 1991; Sham et al. 1992.) (3) Is the finding of an excess of schizophrenia patients in overcrowded inner-city areas entirely due to "drift" as a result of the illness or its prodrome, or is it at least in part a reflection of etiological factors that are more prevalent in such environments? (See Faris and Dunham 1939; Hare 1956; Goldberg and Morrison 1963; Dauncey et al. 1991; Lewis et al. 1992; Takei et al. 1992; Castle et al. 1993*a*.)

The recent renewal of interest in late-onset schizophrenia, which is evidenced by the contributions to this volume of *Schizophrenia Bulletin*, is most welcome. We trust that in the rush to employ new technologies such as magnetic resonance imaging and positron emission tomography in this group of patients, the epidemiologic context will not be forgotten.

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