Influence of Gender in Schizophrenia as Related to Other Psychopathological Syndromes

by Pierre Flor-Henry

Abstract

The evidence indicating that the forms of schizophrenia in men and women represent different morbid states is reviewed. Age of onset and gender are considered to be of fundamental importance in determining the different symptomatological and evolutionary features of the syndrome in the two sexes. Early-onset forms in males are associated with chronicity, absence of familial predisposition for psychosis, and the presence of structural cerebral pathology specifically involving the dominant hemisphere. Later onset forms in females are characterized by more florid symptoms, more affective features, more familial psychosis, and more favorable outcome with no or less pronounced structural cerebral involvement. It is argued that these differential characteristics derive from the differential hemispheric organization of the male and female brain—which also determines the male susceptibility to other psychopathological syndromes such as psychopathy and sexual deviations as well as the excess in women of schizoaffective states, affective disorders, and late-onset schizophrenia.

Fifteen years ago, reviewing developmental and gender-related effects and their etiological contributions to psychosis, neurosis, and epilepsy, Flor-Henry (1974) proposed, heuristically, an original and parsimonious hypothesis to account for various observations:

> Biologically determined, gender related, lateralized differential hemispheric vulnerability distinguishes the male brain from the female brain. In the female the dominant hemisphere is functionally more efficient than the non-dominant hemisphere. In the male the converse is true: the organization of the non-dominant hemisphere is relatively superior to that of the dominant hemisphere. The superiority of girls in language acquisition and skills, the superiority of boys in visuo-spatial abilities, in exploratory drive and in aggressivity derive immediately from this differential cerebral organization. The excess of males exhibiting infantile autism (a cardinal feature of which is complete absence of language, or language retardation), developmental dyslexia (fundamentally a defect in linguistic organization), and childhood epilepsies (essentially because of over-representation of males with left hemisphere lesions, before the age of 2) can all be understood as varying manifestations of this dominant hemispheric vulnerability characteristic of the male gender. In the same manner, aggressive psychopathy associated with the male sex and with diminished verbal as opposed to performance IQ (and in epilepsy with dominant lesions) can be seen as a reflection of the same phenomenon.
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> Similarly, the evidence which suggests that the schizophrenic syndrome hinges on dominant temporal-limbic dysfunction can immediately be integrated with the sex incidence data. The male with dominant hemispheric vulnerability will clearly be more likely to develop the schizophrenic syndrome than the female; but this differential incidence will progressively diminish with maturation. The same mechanism operates in psychopathy, which gradually subsides with age between 30 and 40. This is the very age when the incidence of schizophrenia in males and females approximates. Conversely, depressive neuroses, hinging

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> on non-dominant hemispheric disorganization will predominate in the female gender, who, biologically, have a more vulnerable non-dominant hemispheric organization. The increased incidence of manic-depressive psychosis in females with advancing age is a reflection of the different age of onset of the syndrome, which occurs later in life than schizophrenia, the latter being a disorder of puberty and young adult life. [pp. 148-149]

These issues were later further elaborated (Flor-Henry 1978, 1983, 1985). Reviews which discussed the preponderance of males with early-onset schizophrenia and generally unfavorable outcome were published by Lewine (1981) and Al-Issa (1985). In recent years, accumulating evidence indicates that criminal psychopathy in the male (Wechsler 1958; Prentice and Kelly 1963; Serafetinides 1965; Lishman 1968; Taylor 1969; Sherwin 1977; Lindsay et al. 1979; Wardell and Yeudall 1980; Hare and Frazelle 1981; Yeudall et al. 1981*a*, 1981*b*; Fedora and Fedora 1983; Hare and McPherson 1984; Jutai et al. 1987; Miller 1987; Nachshon 1983, 1988; Nachshon and Denno 1987; Volkow and Tancredi 1987; Hare and Jutai 1988) and sexual deviations (approximately 80% of all sexual deviations occur in males), notably pedophilia and exhibitionism, are all associated with subtle disturbances of dominant hemispheric functions. (Baker 1985; Hucker et al. 1986; Yeudall et al. 1986; Flor-Henry 1987; Cassens et al. 1988; Flor-Henry et al. 1988.)

Age of Onset, Gender, and Type of Psychosis

Rosenthal (1970) reviewed epidemiological information in the United States that illustrates how general these trends are. There were admission rates of 30 per 100,000 for males and 15 per 100,000 for females first hospitalized with dementia praecox in the State mental hospitals in 1933. Basing his calculations on these data and also in first admissions for schizophrenia to the New York State mental hospitals (1929-31), Rosenthal establishes the relative proportions of males and females among all new cases by age. The curves are remarkable: at the age of 25, there are 70 percent male to 30 percent female first admissions; at the age of 35, the sex ratio is equal; by the age of 50, it reverses with two to three females for every male first admission. These trends explain the true but extremely misleading statement often made in the literature that "schizophrenia affects both sexes equally." Since there is now a wide consensus that schizophrenia is a heterogeneous syndrome, it is not likely to be rewarding to confuse a syndrome of early onset that affects males rather than females and—as discussed below—carries a poor prognosis with a late-onset syndrome affecting females and with different outcome and treatment response.

If we consider the differential incidence of schizophrenia and manic-depressive psychoses in males and females, then the increased susceptibility of males to schizophrenia and the more malignant course of this disease in that sex—in contrast to the female preponderance for affective disorders—can immediately be understood as a reflection of the differential hemispheric organization of the male and female brain determined by the testosterone-dependent neurochemical interactions that occur during embryogenesis.

Let us examine the sex-incidence data and the gender-related differences in the schizophrenic and manic-depressive syndromes in more detail. Epidemiological surveys, as McCabe (1975) points out, "have consistently shown differences in age of onset and sex distribution between manic-depressive psychoses and schizophrenia" (p. 320). For example, Ødegård (1971) calculating the "lifetime risk" (first admissions to Norwegian psychiatric hospitals per 100,000 who survive until the age of 90) finds, for the years 1961-65, a male/female sex ratio of 1.35 for schizophrenia and 0.69 for manic-depressive psychoses. McCabe, using demographic data from all psychiatric facilities in Denmark for the year 1971, obtains a male/female ratio of 0.64 for manic-depressive and 1.09 for schizophrenic psychoses (figures for first admissions).

It is important to note here that the schizophrenia sex ratio is near unity because age of onset is not taken into account. For schizophrenia beginning before the age of 40 (required by definition in the Feighner et al. [1972] criteria), there is a striking excess of males for all age subgroups. The sex ratio for onset below age 40 is 1.88 (males = 96, females = 51). Cases beginning before age 20 have a sex ratio of 4.0; those between age 20 and age 30, of 1.7. After age 45, there is a female excess. For schizophrenia, but not for manic-depressive psychosis, the mean age of onset in males is significantly earlier than in females.

Forrest and Hay (1972), who review a number of Scandinavian and German investigations demonstrating the same "sex gap," find in 100 consecutive first admissions for schizophrenia in Edinburgh 33 percent males and only 5 percent females admitted before age 20. The

male/female sex ratio for onset before age 30 was 1.61, but it fell to 0.35 for all cases admitted for the first time between ages 30 and 65 (Forrest and Hay 1971).

These sex differences in the age of onset of schizophrenia are particularly apparent in the most recent studies, which use modern classification systems. Loranger (1984) determined the age of onset in 100 male and 100 female patients who satisfied *DSM-III* criteria for schizophrenia. The mean age of onset of illness, the mean age of onset for first treatment, and the mean age of onset for first hospitalization were all significantly earlier in males than in females (5 years). About 90 percent of male patients became ill before age 30 as opposed to only 20–30 percent of female patients. In contrast, onset of schizophrenia after age 35 occurred in 17 percent of female patients but only 2 percent of male patients. The susceptibility of young adult males to schizophrenia is ubiquitous. It occurs in Ghana (Sikanartey and Eaton 1984), where the point-prevalence rates for ages 25–44 are 1.68/1,000 for males and 0.26/1,000 for females. After age 45, these trends are inverted. It is found in Poland (Majczak et al. 1981) where, in two separate studies, an investigation of schizophrenic first admissions reveals an excess of males, particularly in the 21–25 age range. Polonio (1957), in a study of 3,000 endogenous psychoses in Portugal, documented over a period of 50 years, collected the records of some 600 schizophrenic patients who had been followed for 5–10 years. The worst prognosis was in the group without a family history of psychosis; interestingly, Polonio notes that women had proportionately more complete, and men more merely social recoveries.

The nature of the schizophrenias of (relatively) late onset with female preponderance is suggested by the characteristics of what are now called by the American School "schizoaffective" psychoses or "atypical schizophrenias." A large number of investigations in the last few years have shown that most of these atypical schizophrenias are variants of the manic-depressive syndrome—more precisely, of the bipolar affective psychoses—and are very close symptomatologically to the thought-disordered manias (Clayton et al. 1968; Cohen et al. 1972; Taylor and Abrams 1975; Procci 1976; McCabe 1976; Sovner and McHugh 1976; Tsuang and Dempsey 1979; Pope et al. 1980). Because of the familial associations found in patients with "schizoaffective" disorders, Tsuang (1979) concluded that it is a heterogeneous syndrome with at least two subtypes, one a variant of schizophrenia and the other a variant of affective disorders. Fowler (1978), considering "remitting schizophrenia" as a variant of affective disorder, holds similar views and states that "available data are consistent with the hypothesis that remitting schizophrenia is a heterogeneous mixture of mania, unipolar depression and typical schizophrenia" (p. 76) and that "mania and depression account for the majority of such disorders" (p. 76). Although the schizoaffective group of psychoses generally has a periodic course and favorable outcome, there is a subgroup that shows a chronic unfavorable evolution (Welner et al. 1977). The trend whereby schizophrenia becomes increasingly a female syndrome as the age of onset is delayed is strikingly illustrated in the study of psychoses occurring after age 60, undertaken over a 5-year period by Post (1971) in London. The elderly depressives had a sex ratio of unity, but the schizoaffective syndromes were female in 72 percent of instances and the late paraphrenias (paranoid hallucinosis and schizophreniform and schizophrenic psychoses) had an astonishing 86 percent overrepresentation of women. Marneros and Deister (1984) investigated the clinical features of schizophrenic syndromes first manifested after age 50 and compared these with syndromes first manifested before age 50. The late schizophrenia group was characterized by the prominence of delusions and hallucinations, infrequent disturbance of thought, and a striking excess of females: 85 percent female. This was the case despite the fact that there was an overall excess of female patients in the whole group.

The evidence is extremely suggestive that the curious reversal of the sex ratio in schizophrenia, which shifts from a male excess to a female excess around ages 30 to 40, is to a very large degree brought about by the increasing susceptibility of women, with increasing age, to manifest a variant of the bipolar affective psychoses that has "schizophrenic" symptomatology but is fundamentally (in most instances) a mood disorder. A contributing cause is, perhaps, the fact that aging selectively impairs nondominant hemispheric functions, a process likely to be more pronounced in women, given their initial right hemisphere vulnerability.

Tsuang et al. (1976), in the 10-year investigation of endogenous psychoses carried out in Iowa from consecutive admissions between 1935 and 1944, collected 200 cases of

schizophrenia, 100 bipolar affective psychoses, 225 unipolar affective psychoses, and 85 atypical schizophrenias. The atypical schizophrenias were women in 72 percent of cases and had the same age of onset as the schizophrenia group (28 years), who were males in 52 percent of instances. There was a female excess of 62 percent in the bipolar affective group, but of only 56 percent in the unipolar affective group. Studies which, on the face of it, fail to demonstrate these relationships between gender, course, and symptomatology, on closer examination either do show these effects or are negative for methodological reasons. For example, Gift et al. (1985), who examined 217 patients from two distinct areas, concluded that "race and sex showed no consistent pattern of relationships with psychiatric symptoms, disability and outcome" (p. 1447). In their data, neurotic symptoms were significantly higher in females than in males ($p < 0.003$) but independent of race, while black males had significantly more psychotic symptoms than white males ($p < 0.001$). In the study of a small sample of 64 schizophrenic outpatients compared to 30 controls, 25 of whom suffered from severe depression or mania, Leventhal et al. (1984) concluded that their data failed to demonstrate sex differences "specific and unique to schizophrenia" (p. 464). Given the small numbers involved, this is hardly surprising. Notwithstanding, these authors found a significant main effect for sex and for diagnosis, with the schizophrenic patients manifesting symptomatology earlier than the affective patients. Pursuing their analysis of the "Iowa-500" cohort of psychosis, followed up for 35-40 years, Loyd et al. (1985*a*) reported that gender did not contribute to outcome in schizophrenia, mania, or depression. It should be noted that the majority of the outcome variables considered were sociological rather than psychopathological: marital status, residence, occupation, and psychiatric status. In a related publication, Loyd et al. (1985*b*) found no gender effect among the psychotic relatives of patients with typical and atypical schizophrenia. As the authors point out, the numbers of affected relatives are exceedingly few: the male probands with atypical schizophrenia had two affected female and two affected male relatives, while the female probands had two affected female and six affected male relatives. With such numbers, gender associations, even if present, could hardly be expected to emerge. There is, furthermore, as Lewine (1986) pointed out, a more fundamental flaw in the study. The schizophrenic subjects are statistically deviant because 100 percent have a schizophrenic relative. The evidence is accumulating that the early onset syndrome in males, with negative symptomatology and chronic evolution associated with asocial premorbid personality, is characterized by an absence or a very low frequency of familial psychosis.

Gender and Clinical Features

Leonhard (1980), who had studied for over 40 years typical and atypical psychoses with a clinical precision unique in the literature, noted that "systematic schizophrenics with no, or almost no, family history for psychosis, show the severest forms of schizophrenia, mostly resulting in permanent defects after insidious courses" (p. 439). Leonhard (1979) further noted: "the systematic schizophrenias display a creeping, progressive course while the unsystematic (or atypical, affect laden) forms may go into remission, be periodic and exhibit bipolarity" (p. 155). In institutions with chronic cases, schizophrenic males tend to be ". . . characterized by. . .dull, autistic patients" (p. 422) while females suffering from systematic schizophrenia are "hallucinatory, illusionary patients". . .(p. 422); "the genetic relationships for systematic schizophrenias are very different from those of the unsystematic forms. . .inheritance seems to play only a small role" (p. 441). Goldstein et al. (1990, this issue) cumulated 332 schizophrenic patients, including those with onset after age 45, with the two sexes equally represented. Latent class analysis showed that schizophrenia in the male was likely characterized by (1) poor premorbid adjustment, (2) winter birth, (3) flat affect, and (4) early onset (before age 25). The other subtype, characterized by (1) dysphoric mood, (2) persecutory delusions, and (3) familial loading for schizophrenia, was more likely expressed by females. Seventy percent of the male and 63 percent of the female schizophrenic patients fell into the theoretically expected subtype. For the males, family history and early onset did not differentiate the two groups: hence, low familial loading for schizophrenia and early onset were characteristic of schizophrenic males, regardless of subtype. In a study of 33 normal undergraduates, Raine and Manders (1988) correlated schizoid (schizotypal) personality to a variety of neuropsychological variables and found that it is significantly linked to left hemisphere overactivation, especially in males. Schizoid personality also has been shown to

be overwhelmingly more common in males (Wolff and Chick 1980).

Other observations again point to the fundamental role played by gender in schizophrenia. In a period averaging 37 years, Ciompi and Müller (1976) followed into old age Swiss patients, born between 1873 and 1897, who had been admitted to the psychiatric hospital of Lausanne. Twenty-three percent of the patients with "dementia praecox" and various forms of schizophrenia were hospitalized for more than 20 years. These were principally men. Affleck et al. (1976), in a 12-year followup of 153 schizophrenic psychoses, found that the death rate for men was more than twice that of women and their readmission rate was double. In a 2-year followup of the 1,202 endogenous psychoses entered in the International Pilot Study of Schizophrenia (IPSS; World Health Organization 1973), there were 306 who received a clinical and computer diagnosis of schizophrenia. The patients were derived from the United States, the U.S.S.R., the United Kingdom, Taiwan, India, Nigeria, Colombia, Czechoslovakia, and Denmark. Sartorius et al. (1978) reported that male sex correlated significantly and positively with chronicity, whereas female sex was associated with a remitting course (accounting for 14% and 7% of the variance in outcome variables, respectively). Indeed gender, in the World Health Organization study was the best single predictor of outcome. The same is true in the United States as Goldstein (1988), in the 10-year followup of 90 *DSM-III* (American Psychiatric Association 1980) type schizophrenic patients demonstrated with multivariate regression techniques that women experience fewer and shorter hospitalizations than men. The same was true in a sample of 278 first admission *DSM-III* schizophrenic patients followed for 3 years in Germany (Angermeyer et al. 1989). Goldstein and Link (1988) found significant gender differences in the symptomatological characteristics of 169 *DSM-III* schizophrenic patients. Schizophrenic women expressed more paranoia, impulsivity, sexual disinhibition, and depression. Men were more withdrawn and isolated, suggesting negative symptomatology.

Gender and Neurochemical Characteristics

Abenson (1969) studied the effect of drug withdrawal in 161 chronic schizophrenic patients (105 males, 56 females) with a mean length of illness of 22.3 years. Three months after neuroleptic withdrawal, the males exhibited a significant increase in paranoid belligerence, disorganized thought, and socially embarrassing behavior, while the only change in women was increasing social withdrawal. Not only do schizophrenic females, despite their more florid symptomatology, tolerate neuroleptic withdrawal better than males, but their symptomatic improvement is maintained with, on the average, half the amount of chlorpromazine (437 mg) required by schizophrenic males (812 mg) (Seeman and Lang 1989). In this latter investigation of schizophrenic outpatients, 26 males and 26 females were matched for age at the time of the survey: the age of onset was significantly earlier in males, as was their age at first hospitalization and, again, quite significantly, the females were employed and the males unemployed. The males had significantly more episodes requiring hospitalization. The greater degree of improvement of schizophrenic women, on substantially lower doses of neuroleptics, has led some authors to attribute the phenomenon to an endogenous antischizophrenic factor present in women, but not in men (e.g., estrogens). Indeed, it has been shown that estrogens desensitize the dopaminergic response by an inhibitory action, at a step following the dopamine receptor in the striatum, nucleus accumbens, and frontal cortex (DiPaolo et al. 1979) and that estradiol has potent antidopaminergic activity at the pituitary level on prolactin release (Raymond et al. 1978). However, as Seeman and Lang (1990, this issue) point out, neuroleptics, via the hypothalamic-pituitary axis, inhibit ovarian estrogen output: thus, the beneficial estrogenic mediated antidopaminergic action postulated would be, to a certain extent, canceled. Furthermore, on this hypothesis, one would expect women to be relatively protected against other morbid states associated with hyperdopaminergic activity, such as mania or amphetamine psychosis. This does not appear to be the case. Nonetheless, it is probable that complex sex-steroid-cerebral interactions are of relevance to these issues. It is probably not a coincidence that these hormones bind essentially on those anterior limbic structures whose dysregulation modulates psychotic phenomena. Testosterone-binding neurons are concentrated in the hypothalamus and amygdala, while estrogen-concentrating neurons are almost exclusively located in layers V and VI of the frontal and cingulate cortex (in the rat). Further, androgens and estrogens influence differentially the right and the left

hemisphere. Since Ounsted and Taylor (1972) first formally expressed the idea, the notion that one of the functions of testosterone during embryogenesis is to delay the pace of development of the left hemisphere has been adopted by Geschwind and Behan (1982) to explain the associations among immune system dysfunction, sinistrality, and dyslexia in boys. The Geschwind-Behan hypothesis has recently been indirectly confirmed by Hugdahl et al. (1989). Altemus et al. (1989) showed that the right ear advantage for fused, single response dichotic stimuli is significantly lower premenstrually and greater during the postmenstrual phase of the cycle. Thus, during the luteal (or progesterone) phase of the cycle, there is a relative decrease in left hemispheric functions. These authors review other evidence indicating that in men verbal fluency is enhanced and spatial orientation impaired after injections of luteinizing hormone-releasing hormone. Levels of follicle-stimulating hormone are negatively correlated with visuospatial skills in both sexes and positively correlated with verbal fluency in women (Gordon and Lee 1986; Gordon et al. 1986).

That different neurochemical processes are involved in schizophrenic males and schizophrenic females is also suggested by the different associations of reduced platelet monoamine oxidase (MAO) activity in men and women (and in blacks and whites). Meltzer and Zureick (1987) found that reduced MAO activity was associated with paranoid schizophrenia characterized by auditory hallucinations in males but not in females, and in blacks but not in whites. Paranoid schizophrenic males, with auditory hallucinations, but not males with undifferentiated schizophrenia, exhibited lower MAO activity. This was not the case in women, whether of the paranoid or undifferentiated subtype. These are the conclusions of the authors. The more general observation in their data is that when race and schizophrenic subtype are collapsed, males with auditory hallucinations have a significant reduction of activity compared to nonhallucinating males, whereas there are no such correlations in schizophrenic females. The implications of these findings remain to be worked out. They can probably be related to the report of Murphy et al. (1977) in normals showing that males with low MAO activity have deviant hypomania, psychopathy, and schizophrenia scores on the Minnesota Multiphasic Personality Inventory (MMPI; Golden and Meehl 1979), but low MAO females do not demonstrate these features. Thus, there emerges a vulnerability specific to males with low MAO activity, expressed across several psychopathological dimensions: auditory hallucinations and certain forms of deviant personality.

Neurobiological Characteristics of Schizophrenic Males

In a prospective study of 165 children who had been referred to a child guidance center in New York City, Gardner (1967) isolated 60 males who later were hospitalized with the diagnosis of schizophrenia (of whom 32 became chronic) and 48 females with schizophrenia (of whom 25 had a chronic illness). They were compared for anxiety, phobias, obsessive-compulsive traits, and hysterical traits with controls who had been seen as children at the center but were never subsequently hospitalized for psychiatric illness or jailed. The male children who later developed schizophrenia had significantly higher scores for anxiety, phobias, and obsessions than did the control boys, whereas the females who developed schizophrenia did not differ, on these variables, from the control girls. A number of studies discussed by Wagner and Stegeman (1969) show that the premorbid personality of boys—but not girls—who later develop schizophrenia is not schizoid, but of unsocialized aggression. Schizoid personality, however, is highly associated with the male gender (Wolff and Chick 1980). The personality of monozygotic twins discordant for schizophrenia is abnormal in a high proportion of cases, the type of abnormality depending on the sex. The males show character disorder and the females, neurotic symptoms (Cadoret 1973). There is a correspondence between these personality traits in male monozygotic twins discordant for schizophrenia and in the schizophrenia spectrum of psychopathology observed in about 20 percent of the offspring of schizophrenic parents which Rieder (1973) divided into two main categories: a withdrawn, schizoid type and a hyperactive, asocial delinquent type.

We see, once more, in these character disturbances the strong male association. The ever-present influence of the male gender in schizophrenia is revealed in an even more unusual way in the study of hyperactivity and neurological soft signs in the offspring of patients with "continuous schizophrenia" undertaken by Rieder and Nichols (1979). They found that 8 of 29 male offspring tested neurologically and psychologically at age 7 were

hyperactive and exhibited neurological soft signs—significantly more than did the control boys. The 15 female offspring did not differ from controls on any of these measures. Here the sons, but not the daughters, have a specific cerebral vulnerability, presumably of constitutional-developmental origin. Another example of this fundamental male vulnerability is provided by Nasrallah and Wilcox (1989). They observed that in 199 schizophrenic patients extracted from the Iowa-500 series and in which both sexes were equally represented, male subjects suffered serious brain injuries in childhood (before age 10) and had more negative symptomatology significantly more often than women. In males, the interaction of brain injury and absence of family history for psychosis was significant in contrast to women who were characterized by the absence of brain injury and the presence of family history for psychosis. There is thus a considerable weight of evidence that the malignant form of schizophrenia, of early and insidious onset, which runs a chronic course, is a syndrome to which the male is neurobiologically vulnerable.

Influence of Diagnosis on Sex Ratio

Taylor and Abrams (1978), using strict research criteria for schizophrenias analogous to dementia praecox, find that hospital admission prevalence of schizophrenia is quite low (of the order of 6%) and review many inpatient and outpatient studies that report similar figures. These authors discuss a number of population studies where, when strict criteria are applied, the age-corrected morbidity risk for schizophrenia oscillates between 0.4 percent and 0.6 percent. In addition, they comment that if strict criteria are applied, not only to the patients but also to their first-degree relatives, then the morbidity risk for schizophrenia in the first-degree relatives is extremely low (2.6% in the Kety et al. [1968] biological relatives of adoptive schizophrenics, 2.7% in the blind family history study of relatives of Winokur et al. [1974], and 2.9% in the Icelandic study of Karlsson [1973]).

Generally speaking, the stricter the criteria for schizophrenia, the greater the male excess. Lewine et al. (1984), studying the contribution of the diagnostic system to the sex distribution in 387 patients (classified schizophrenic according to six systems), found an overall male excess of 1.4:1 (male/female ratio). However, the ratio was near unity with the New Haven Schizophrenia Index (Astrachan et al. 1972) (1.1:1, NS), became 1.4:1 (NS) with first-rank symptoms, 1.8:1 ($p < 0.02$) with Taylor and Abrams (1978) criteria, 2.8:1 with Research Diagnostic Criteria (Spitzer et al. 1978) ($p < 0.02$), and 7:0 with the Feighner et al. (1972) criteria ($p < 0.02$) (Lewine et al. 1984). Focusing on the degree of diagnostic concordance as a function of sex, in this series, Burbach et al. (1984) found that men were clearly more concordant than women, across the various diagnostic classifications. Notably the four patients who were classified as having schizophrenia in all the systems were three males, with onset before age 19, poor premorbid personality, and scholastic underachievement. The fourth was a woman, with good premorbid personality, onset after age 30, and strong affective symptomatology. The authors concluded that "To the extent that diagnostic concordance reflects an underlying common trait among diagnostic criteria for schizophrenia (Young et al. 1982), the results suggest that men, as predicted, are more typically schizophrenic than women" (Burbach et al. 1984, p. 479).

Gender and Developmental Aspects

It is well known in a statistical sense that in schizophrenic populations, compared to controls, there is a significant excess of birth complications, an over representation of first or last born, and an increased incidence of structural cerebral changes: dilation of the ventricular system, cortical atrophy, or both. What is less widely appreciated is that often these various associations are significant in schizophrenic males but not in schizophrenic females. Mednick (1970) followed 207 children at risk for schizophrenia. Twenty of the children presented with psychiatric symptoms by age 15. Pregnancy and birth complications had been noted in 70 percent of the sick group and 15 percent of the well group. Mirdal et al. (1974) drew attention to the fact that the pregnancy-birth complications effect was statistically significant only for the first-born male children. Granville-Grossman (1966) found that only schizophrenic males were more often last-born, while Sundararaj and Rao (1966) reported a shift toward early ordinal birth ranks that was only true for males. In Brazil, Térzis (1986) found an excess of first-born children in both schizophrenic males and schizophrenic females, a relationship more pronounced in males.

Takahashi et al. (1981) studied 257 schizophrenic patients with computed tomography (CT). Cerebral

atrophy of the dominant hemisphere (temporal lobes, left > right) was correlated with defect symptomatology and blunted affect and was significantly more pronounced in males. Overall CT scan abnormalities were significantly associated with the male sex, although in both sexes hallucinations were associated with left temporal cortical atrophy. Andreasen's (1984) findings supported increased ventricle-brain ratio (VBR) among male but not female schizophrenic patients. Haas et al. (1989) strikingly verified these relationships in the neuropsychological and CT scan survey of 66 male and 52 female schizophrenic patients, in which VBR and clinical variables were correlated. The schizophrenic males were significantly more often single, younger, and younger at onset and first hospitalization and exhibited more blunted affect than schizophrenic females. They had more deficit on the Wisconsin Card Sorting Test (Heaton 1981), on Trail Making Test A and B (The Adjutant General's Office 1944), and on the Rey Auditory Verbal Learning Test (Taylor 1959; Rey 1964; Lezak 1983) (i.e., showed greater impairment than females for frontal and left temporal functions). The VBR was more abnormal in males than females and the left/right VBR was significantly greater in males (0.8) than in females (0.097), a difference showing relatively greater left hemisphere atrophy in schizophrenic males, significant at the 0.0001 level of probability. The observations of Haas et al. are nicely in line with the report of Keefe et al. (1989), who measured in 69 chronic schizophrenic males the left/right VBR and found that premorbid asociosexual functioning was significantly correlated with the degree of left/right lateral ventricular asymmetry: the greater the premorbid impairment, the greater the left/right ventricular asymmetry. It is important to note that the VBR did not show any correlations with premorbid functioning indices, a relationship which emerged only with the left lateralized index.

Psychopathological Characteristics of Schizophrenic Males: Specific or Nonspecific?

The evidence reviewed indicates that the schizophrenic syndrome in males is in many respects different and more severe, associated with a greater degree of cerebral dysfunction than the equivalent syndrome affecting women. This effect, however, is not specific to schizophrenia but is a reflection of the special vulnerability of the left or dominant hemisphere in the male, compared to the female. Thus, in all the psychopathological syndromes that are derivative of disturbed or altered dominant hemispheric systems, there is a male preponderance: autism, psychopathy, sexual deviations, and (probably) early onset obsessive-compulsive states.

A curious and striking example of the male's left hemisphere vulnerability is seen in temporal lobe epilepsy occurring as an aftermath of febrile seizures and convulsive hypoxia (mesial temporal sclerosis). Taylor and Ounsted (1971) showed that the probability of occurrence of left and right mesial temporal sclerotic lesions in boys and girls after convulsive hypoxia—an apparently generalized cerebral insult—was far-reaching. They demonstrated that the left hemisphere of the male was more often affected than that of the female, in whom the probability of a right or left brain lesion was about equal, because in the male the left hemisphere was at risk for a longer period (first 4 years of life) than in the female (first 2 years of life).

Evidence from epileptic studies first revealed the male-left hemisphere association in psychopathy. Serafetinides (1965) showed that aggressive psychopathy in epilepsy was related to early onset epilepsy of the dominant hemisphere in males. The relationship of aggressive, paranoid, psychopathic personality to temporal lobe epilepsy of the left or dominant hemisphere has been confirmed by Taylor (1969), Sherwin (1977), and Lindsay et al. (1979). In the prospective Oxford series of Lindsay et al. (1979), 100 subjects with pure limbic epilepsy were followed from birth. Of the 87 patients surviving at age 15, 12 had exhibited severe antisocial/aggressive behavior; in all 12, the focus was contralateral to the preferred hand—very significant lateralization. Ten of the 12 were males. Catastrophic rage reactions were significantly associated with the onset of epilepsy before the age of 1 year and with a significant decrement of verbal IQ for both sexes, again demonstrating disorganization of dominant hemisphere systems. Investigations of large samples of aggressive psychopaths (homicide, rape, and physical assault) (Yeudall 1977; Yeudall and Fromm-Auch 1979) with an extensive neuropsychological battery consisting of 32 tests revealed that in this group, which satisfied Cleckley's criteria (Cleckley 1955) for primary psychopathy, the neuropsychological profile was abnormal in 90 percent of cases. In 72 percent, the pattern of cerebral dysfunction was bilateral frontal, left > right, and left temporal. A reduced verbal compared to performance IQ was found, with a particular

vulnerability of the Comprehension subtest on the Wechsler Adult Intelligence Scale (WAIS; Wechsler 1958) (Yeudall et al. 1981*a*, 1981*b*). Wardell and Yeudall (1980) found that psychopaths with the largest verbal/performance discrepancy in a large sample were characterized by elevations on the psychopathy and schizophrenia scales of the MMPI and by an excess of sinistrality in 14 percent. Fedora and Fedora (1983) used a very extensive neuropsychological battery to compare psychopathic criminals, nonpsychopathic criminals, and carefully matched controls. The psychopathic and nonpsychopathic criminals differed from the controls only on neuropsychological variables considered to be left hemisphere and frontal impulsivity markers. Thus, psychopathy arises because of disruptions of left temporal neural systems brought about by epilepsy early in life, or through genetic-constitutional factors impinging on these critical cerebral regions in the male. It is worth noting that the psychopaths with the largest verbal decrement compared to performance IQ and with excess sinistrality—both indices of left hemisphere dysfunction—showed elevations on both the psychopathic deviate and schizophrenia scales of the MMPI. A commonality between psychopathy, certain forms of schizophrenia, and dominant dysfunction is thereby implied. The underlying affinity between the two syndromes is also suggested by a number of the clinical characteristics common to the two syndromes: the asocial aggressive premorbid personality of early onset, poor prognosis schizophrenias in males; the pseudopsychopathic schizophrenias described in earlier classifications; the "schizophrenia spectrum" disorders found principally in the male first-degree relatives of schizophrenic patients; the personality characteristics in monozygotic twins discordant for schizophrenia where the nonschizophrenic twin, if male, is psychopathic and, if female, neurotic (Cadoret 1973). Again, both syndromes sometimes share a startling absence of human empathy. Wechsler (1958) had noted that adolescent male psychopaths have a relative deficit of verbal compared to performance IQ. Nachshon (1983) reviewed the numerous studies confirming this effect in delinquents, sociopaths, acting-out juveniles, criminal offenders, and female delinquents (Bernstein and Corsini 1953). Prentice and Kelly (1963), in a review of 24 studies, concluded that delinquents were similar to normals for performance IQ but were significantly lower for verbal IQ. Yeudall et al. (1981*a*, 1981*b*) found a significant reduction of verbal/performance IQ of 9 points in psychopaths, 7 points in rapists, and 6 points in assaultive criminals. Homicidal prisoners, however, did not exhibit the verbal < performance pattern. For purposes of comparison, the verbal IQ of 128 patients with unilateral left hemisphere lesions was 87 and the performance IQ 91, while in 204 patients with unilateral right hemisphere lesions the average verbal IQ was 97 and performance IQ 85 (Woods 1980). Yeudall et al. (1987) observed a significant increase in left parietal alpha power in the eyes-closed condition in 10 murderers and 4 individuals with a history of repetitive physical violence, a finding that might suggest a defect of left hemisphere inhibitory regulation. Seventy-five percent of 15 violent-aggressive outpatients showed left-sided asymmetry of brainstem auditory evoked responses. Hare and Frazelle (1981) found that in the tachistoscopic presentation of stimuli requiring complex semantic processing, psychopaths, unlike normals, failed to show a right visual field superiority: this would be predicted by a hypothesis of left hemisphere dysfunction (cited by Nachshon 1983). Hare and McPherson (1984), in a verbal dichotic listening task under divided or directed attention, showed that psychopaths had a smaller right ear advantage than nonpsychopaths, a result that, once again, is consistent with a left hemisphere deficit in psychopathy. The third lateralizing observation published by Hare and McPherson (1984) relates to the slower electrodermal recovery time for the left hand to tone signals of high intensity found in psychopaths. Nachshon (1988) studied 127 criminals with two dichotic tasks: verbal stimuli (digits) and analytically processed nonverbal stimuli (tones). The prisoners consisted of the following three groups: murderers, violent offenders, and nonviolent criminals. There were no significant differences among the groups on the digit test; however, for the tone test (identification in one ear of one of four tones as identical to target tone, previously delivered to one of the ears), the murderers and nonviolent offenders showed a right ear advantage—similar to normals—while the violent offenders had a left ear advantage. In addition the violent offenders had a significant decrease in right ear scores compared to the other offenders with no decrease in left ear scores. These results indicate clearly the presence of a unilateral deficit in the left hemisphere of violent offenders. Nachshon explains the paradox of the murderers being similar to the nonviolent criminals

by the fact that they were usually nonviolent individuals guilty of a single criminal act, in contrast to the violent offenders, most of whom were recidivists. Gabrielli and Mednick (1980) related lateral preference (measured in 1972) to subsequent criminal behavior (1978). Sixty-five percent of the sinistrals versus only 30 percent of the dextrals were arrested once; 33 percent of criminals with multiple arrests were sinistral, as compared to 11 percent of those with a single crime and 7 percent of nonoffenders.

The excess of males afflicted by the syndrome of infantile autism is well known and universal. Although the relationship between schizophrenia and autism is controversial, profound affinities link the two syndromes: in both there is a striking excess of males, in both there is an overrepresentation of first and last born in the sibship, in both vestibular abnormalities are found, in both there is an excess of sinistrality, and in both there are genetic-constitutional ("idiopathic") and acquired forms. Rutter and Lockyer (1967) and Rutter et al. (1967) have shown that a central aspect of the syndrome is the absence, or impairment, of language functions. In keeping with this, DeMyer et al. (1974) found that the mean verbal IQ of a group of 115 autistic children was 35, while the performance IQ was 50. Of great interest was the observation that there was a positive relationship between the ability to relate emotionally and verbal IQ. A neuropsychological study by Hoffmann and Prior (1982) of 10 high-functioning autistic children (average IQ = 87) (subjects selected to eliminate the nonspecific impact of intellectual retardation), who were compared to mental-age-matched and chronological-age-matched children, showed that the autistic group was significantly impaired on left hemisphere tests. In particular, they had significant deficits on Wechsler Intelligence Scale for Children (WISC; Wechsler 1974) vocabulary, comprehension, and similarities subtests, while they had normal scores on WISC block design and object assembly subtests and a target test. The importance of dominant hemisphere dysfunction in autism was confirmed by Hauser et al. (1975), who showed by air-encephalographic investigation that a group of autistic patients were characterized by central atrophy of the dominant temporal lobe.

When all sexual deviations are considered, there is an enormous excess of afflicted males, of the order of 80 percent. Some sexual deviations are present uniquely in males (i.e., exhibitionism and voyeurism). Fetishism is extraordinarily rare in women. Theoretically, therefore, left hemisphere dysfunction should be present in the sexual deviations, given the astonishing susceptibility of males to these disorders compared to females. There is evidence that this is the case. Hucker et al. (1986) reported neuropsychological and CT scan evidence of left hemisphere dysfunction in pedophiles. Neuropsychological studies in exhibitionism (Baker 1985; Yeudall et al. 1986) also revealed the presence in that disorder of discrete, focal, but extremely consistent neuropsychological deficits implicating dominant frontotemporal regions (reviewed by Flor-Henry 1987). Cassens et al (1988) noted the presence of electroencephalographic (EEG) and evoked potential (auditory and visual) abnormalities that were either bilateral or left frontotemporal in all the homosexual paraphilias that they investigated. Flor-Henry et al. (1986, 1988), in the statistical quantitative EEG investigation of two series of exhibitionists, observed that EEG power and coherence were significantly different than in healthy controls during verbal cognitive activation, but did not differ during spatial cognitive activation. A subtle dysfunction of neurophysiological processing of the dominant hemisphere is thereby suggested. Neuropsychological and EEG studies of a large series of pedophiles (n = 96) revealed significant bilateral frontal and left temporal dysfunction on neuropsychological indicators and a pattern of EEG parameters almost identical to that seen in the exhibitionists (Flor-Henry et al. 1989; Lang et al., in press). The general implications of this new research on the cerebral determinants of sexual deviations have been discussed by Flor-Henry (1989).

A number of features of the obsessional syndrome are remarkably similar to those seen in schizophrenia. Birth trauma or perinatal injuries are associated with later schizophrenic breakdown; Capstick and Seldrup (1977) found a history of abnormal birth events in one-third of unselected obsessionals. In schizophrenia there is a statistically significant excess of first- or last-born children in males. Snowdon (1979), in an analysis of birth order in obsessional neurosis (n =156) of whom 70 were males matched against 500 male and 500 female controls matched for sex, year of birth, and social class, found a significant excess of first-born males among the obsessionals. In schizophrenia, the earlier the age of onset, the greater the male incidence and the more likely a chronic course. Rasmussen and Tsuang (1986), although they had more women

(two-thirds) than men in their clinical-demographic survey of 44 obsessionals, reported that a deteriorating course was more likely in men with early onset of illness. Men had a significantly earlier age of onset (15.5 years) than women (23 years)—again strikingly similar to the age of onset-sex characteristics of schizophrenia (both shifted, of course, to an earlier onset in the obsessions). Hollingsworth et al. (1980), reviewing 8,367 child and adolescent inpatients and outpatients in Los Angeles between the years 1959 and 1975, found 17 cases meeting strict criteria for the obsessional syndrome: 13 were male and only 4 female. In a study of childhood obsessive-compulsive disorders, Rapoport et al. (1981) have a first series of 11 patients (average age 14), 9 of whom are boys. With the expansion of the series to 17 adolescents, there are 14 boys and 3 girls (Behar et al. 1984). Adams (1973) collected 49 children with obsessions, over a 12-year period, from a clinical pool of about 4,000 in which the incidence was four times greater in boys than in girls: 39 boys and 10 girls. Honjo et al. (1989) reported a sex ratio (male/female) of 1.7:1 in childhood obsessions but cited another Japanese study with a sex ratio of 3.2:1 (Wakabayashi et al. 1982). Swedo and Rapoport, as cited by Gittelman-Klein (1989), reported 80 percent of males in a sample of 70 children in whom the obsessional illness started before age 8.

Conclusion

The evidence is persuasive that the schizophrenic syndrome in men and women produces different morbid states. The age of onset, the symptomatology, the familial predisposition for psychosis, the presence or degree of structural cerebral changes, the neuroleptic response, and the evolution of disorder are significantly different in schizophrenic males and females. The later the age of onset, the more florid the symptomatology and the greater the female excess. The earlier the age of onset and the stricter the definition for schizophrenia, the greater the male excess. Irrespective of age of onset, women are more at risk for the expression of acute and atypical schizophrenia, with prominent affective features, both schizomanic and schizodepressive (variants of the bipolar mood psychoses). Constitutional-developmental factors impinging on vulnerable dominant hemispheric neural systems in the male brain appear to be of crucial importance in the determination of schizophrenia manifested later in ontogeny in that sex. These factors, however, are not specific to schizophrenia and are found in a variety of other psychopathological states: autism, psychopathy, sexual deviations, and, in all probability, in very early onset obsessive-compulsive states. In females, familial-genetic predisposition to "mood psychosis" interacting with the more vulnerable nondominant hemispheric systems appears to be a major etiological determinant.

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