rates of violence] are legion.1,2(p400) Czobor and Volavka's hypothesis that the downward trend may have been due to the systematic attrition of a certain subgroup of patients is interesting, as are many other hypotheses that could have been considered. To identify substantively meaningful subgroups of patients who are similar in their personal characteristics and individual trajectories of violence over time is a worthwhile pursuit; however, such a pursuit requires different methods with their own limitations and difficulties.

Point 3, the purpose of including time at risk as a covariate in a logistic regression was to examine if the significant downward trend in violence would maintain after the variation in violence accounted for by time at risk was controlled. We controlled for time at risk by entering it into the model first and then examining the independent contribution of the time trend. If we had been making inferences regarding the true (ie, unbiased) slope estimate associated with the downward trend for the full population of patients based on a single regression model, we would have confronted the issues of statistical independence and bias raised by Czobor and Volavka.

We appreciate this opportunity to respond to these comments.

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Androgen Replacement in a 48, XXYY-Male Patient

A 32-year-old man was admitted to our institute in January 1995. A 48, XXYY karyotype had been diagnosed at the age of 6 years, subsequent to delayed speech development. Because of the primary hypogonadotropic hypogonadism common in this disorder, androgen replacement was first considered in 1988. The rationale was to prevent somatic consequences of hypogonadism such as osteoporosis and muscle wasting. However, this proposal was discarded by a counseling psychiatrist because “...androgen replacement would be too risky considering the patient’s labile personality structure. ...” For similar reasons, 3 more clinics refused to initiate androgen replacement therapy. Six months prior to admission to the hospital, the patient developed increasing tiredness, sleeping 10 to 12 hours on weekdays and up to 16 hours on weekends. Therefore, he was finally referred to our institute for reevaluation of androgen replacement therapy.

The tall (192-cm) and obese (120-kg) patient presented with prominent hypogonadal signs such as gynecomastia, scanty pubic hair, and clearly reduced testicular volume (2 mL). Initial laboratory and bone density values are given in the Table. Findings from psychopathological examination were normal, especially since no signs of aggressive behavior could be established. Sexually, he reported nightly erections and a masturbation frequency of 2 to 3 times per week. On neuropsychological testing, the patient’s IQ was 90; in particular, he had difficulties conducting multiple tasks simultaneously. During the following 2 weeks, the patient showed irritability when confronted with difficult problems. This behavioral pattern was confirmed by colleagues at his workplace, who, however, denied that he exhibited antisocial, aggressive, or sexually offensive behavior.

Since February 1995, the patient received 250 mg of testosterone enanathate intramuscularly every 4 weeks. With this regimen, endocrine and bone density parameters stabilized (Table). Subsequently, no adverse behavioral changes were observed; in particular, no increased aggressivity or hypersexuality occurred during the entire 18-month follow-up period as evaluated by regular interviews. Moreover, a clear decrease in daytime sleepiness and apathy was noted.

Phenotypic males with the XXYY karyotype exhibit hypogonadism that may lead to generalized osteoporosis and muscle wasting.1,2 Since the early 1960s, it has been suggested that the presence of 2 Y chromosomes might predispose to aggressive behavior. However, the most thorough study on this topic to date neither supported the notion that men with sex chromosome anomalies are particularly violent or aggressive, nor that testosterone is a mediating factor for criminal behavior.3 Moreover, androgen replacement in hypogonadal men using physiological or modestly supraphysiological doses of androgenic steroids have rarely resulted in socially disruptive behaviors. Major mood disturbances, including enhanced irritability and aggressivity,
as well as mania, hypomania, and major depression have only been related to very large doses of anabolics abused by athletes. Also, hypogonadal men with Klinefelter syndrome receiving oral androgens showed only a moderate increase in sexual interest; no effects on self-reported mood or energy were noted. Thus, we do not consider possible psychopathological sequelae of androgen replacement in XXXY male subjects to outweigh their beneficial effects, and we therefore suggest initiating treatment in these patients as early as possible.

Structural Brain Changes in Schizophrenia

I read with interest the excellent study reported by Zipursky et al in the June 1998 issue of the Archives. However, I would like to focus on one aspect that could be misinterpreted. The fact that they find reduced gray matter in “first episode psychosis” does not mean that this structural deviance is neurodevelopmental and due to a fixed lesion early in life. “First episode” does not mean “at the onset” but only that there has been no previous recovery and then subsequent exacerbation of symptoms. Illness duration prior to the magnetic resonance imaging scan in the Zipursky et al study is stated as being between 0.04 and 15 years. Thus, it could be that brain change has been occurring over time, reducing gray matter during the course of illness subsequent to its onset and prior to the scan. Some evidence for this now comes from many recent studies.2-5

On the other hand, gray matter reduction may certainly be occurring during the early stages of an illness, probably during the prodromal stage before the onset of positive symptoms since we also reported that detectable gray matter reduction was present in a select group of schizophreniform patients who at a 2-year outcome evaluation were diagnosed as having chronic schizophrenia.6 We speculate that the reduction in gray matter was probably a continuous process since it was not as great as that seen when the brains of similar patients were scanned in the chronic phase of illness.7

In summary, there is now evidence of a continuous deteriorating brain process that leads to the structural deviations seen on magnetic resonance imaging scans of chronic patients and the solely “neurodevelopmental” view needs to be reconsidered.

In reply

DeLisi correctly points out that our study does not establish that the brain abnormalities found in schizophrenia are neurodevelopmental in origin or due to a fixed lesion. We cannot, however, agree with the suggestion made by DeLisi that “reduction in gray matter was probably a continuous process since it was not as great as that seen when similar patients were scanned in the chronic phase of illness.” First, it is not at all clear that our first episode subjects from Toronto, Canada, were similar to chronically ill subjects recruited from a veterans’ hospital in California; for this reason, we highlighted the possibility that the smaller effect size found in first episode patients might be due to a selection bias. Second, the structural brain abnormalities found in schizophrenia have not generally been found to be associated with the duration of illness in studies of either chronic, or first episode patients. Third, despite recent evidence that progression of ventricular enlargement may take place over some part of the course of the illness, there is no evidence that this is a process that is continuous over the entire course of the illness. Finally, there is no reason to assume that all structural brain findings in schizophrenia relate to a single pathophysiology. Woods et al have suggested that the brain abnormalities found in schizophrenia might be best explained by a 2-process model involving both static and progressive abnormalities. Progressive ventricular enlargement during the course of schizophrenia might also be due to the effects of aging, alcohol, nutrition, medication, or an impoverished environment.