

Etiology of Structural Asymmetry in Schizophrenia: An Alternative Hypothesis

To the Editors:

Abstract

During normal development of the fetal brain, the left hemisphere lags behind the right hemisphere in intrauterine growth, causing the left hemisphere to be smaller than the right hemisphere throughout the early and mid-prenatal period. By the end of the second trimester, the right hemisphere has achieved almost full-term size; thus second-trimester injuries affecting neurons, that is, anoxic, ischemic, toxic, or infectious insults that are systemic and bilateral, will affect the left hemisphere more than the right hemisphere. While other explanations for brain asymmetries in schizophrenia have been proposed, the embryological literature is consistent with the hypothesis that a prenatal injury may be one etiological factor in producing the structural brain asymmetries seen in psychotic adult patients.

It has been established beyond doubt that subtle structural abnormalities in brains of patients with schizophrenia can be found in both hemispheres (Suddath et al. 1990). As Crow (1990) has recently pointed out, however, the research literature consistently suggests that the subtle brain tissue loss is slightly, but significantly, more marked in the left hemisphere. Crow (1990) deftly makes the case for a laterality gene as a purely genetic explanation for this structural asymmetry. We would like to offer an alternative hypothesis.

During normal development of the fetal brain, the left hemisphere lags behind the right hemisphere in intrauterine growth (Fontes 1944; Chi et al. 1977), causing the left hemi-

sphere to be smaller than the right hemisphere throughout the early and mid-prenatal period. The left hemisphere catches up with the right hemisphere by the third trimester and is approximately equal in size to the right hemisphere at term.

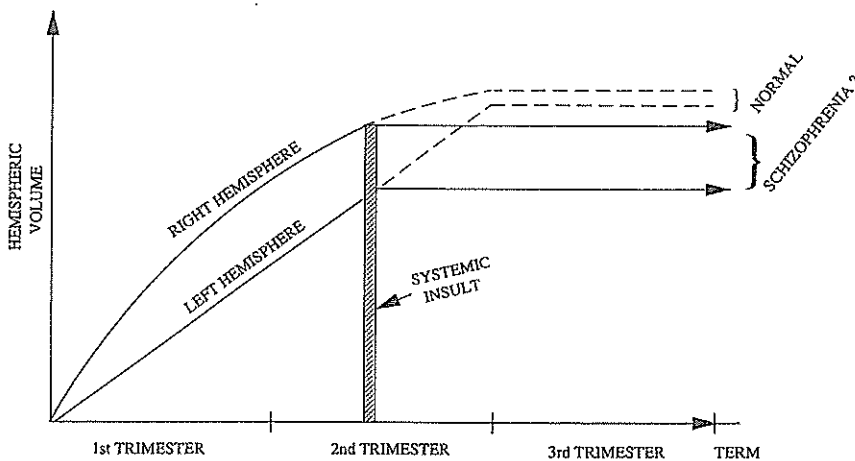
By the end of the second trimester, the right hemisphere has achieved almost full-term size. Thus, injuries affecting neurons during the second trimester, that is, anoxic, ischemic, toxic, or infectious insults that are systemic and bilateral, will affect the left hemisphere more than the right hemisphere. This concept is schematically illustrated in figure 1.

Crow has suggested that schizophrenia is a "laterality gene disorder." This theory is not implausible, nor is the possibility that psychosis can occasionally result from interaction between genes and old unilateral brain injuries (Bracha et al. 1989). As many researchers have recently pointed out (e.g., Gottesman et al. 1987), however, the weight of the evidence suggests that schizophrenia is multifactorial and results from an additive or synergistic effect of a polygenetic predisposition and multiple environmental insults. Such environmental insults probably include systemic neurotoxic or infectious insults that occur during the second trimester (Mednick et al. 1988; Lohr and Bracha 1989).

Thus, structural asymmetry may be merely an artifact of the timing of the insult and may be most useful as a marker of the timing of the insult. Schizophrenic patients with structural brain asymmetry may have suffered an earlier brain injury. As a rule, during the prenatal and perinatal period, earlier injuries have a greater potential influence on subsequent brain development than do injuries occurring later in development. See Nowakowski (1987) for discussion of

Figure 1. Schematic illustration of the effect of a brief mid-second-trimester injury on left and right hemispheric volume

IMPLICATIONS OF NORMAL FETAL DEVELOPMENT FOR THE
PATHOGENESIS OF STRUCTURAL BRAIN ASYMMETRY IN SCHIZOPHRENIA



this "Cascade Principle" in brain development.

The following two findings are consistent with this hypothesis. First, asymmetric enlargement of the lateral ventricles—left more enlarged than right—has been found to correlate with a more malignant Kraepelinian course of schizophrenia (Losonczy et al. 1986; Keefe et al. 1987). Second, the left temporal lobe may be the area of the greatest tissue loss in schizophrenia. This second finding may be explained by the fact that the temporal cortex is the last cortical area in each hemisphere to complete neuronal migration (Crow 1990).

In summary, the laterality literature seems to be consistent with the theory that a prenatal injury may be one etiological factor in adult psychoses. The embryological literature also appears to support the hypothe-

sis that a prenatal injury may contribute to the etiology of structural brain asymmetries seen in psychotic adult patients.

References

- Bracha, H.S.; Lyden, P.D.; and Khansarinia, S. Delayed emergence of striatal dopaminergic hyperactivity after anterolateral ischemic cortical lesions in humans: Evidence from turning behavior. *Biological Psychiatry*, 25:265-274, 1989.
- Chi, J.G.; Dooling, E.C.; and Gilles, F.H. Gyral development of the human brain. *Annals of Neurology*, 1:86-93, 1977.
- Crow, T.J. Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophrenia Bulletin*, 16:433-443, 1990.
- Fontes, V. *Morfologiae do Cortex Cerebral (Desenvolvimento)*. Lisbon: Instituto Antonio Orelia da Costa Ferreirs, 1944.
- Gottesman, I.I.; McGuffin, P.; and Farmer, A.E. Clinical genetics as clues to the "real" genetics of schizophrenia (a decade of modest gains while playing for time). *Schizophrenia Bulletin*, 13:23-47, 1987.
- Keefe, R.S.; Mohs, R.C.; Losonczy, M.F.; Davidson, M.; Silverman, J.M.; Kendler, K.S.; Horvath, T.B.; Nora, R.; and Davis, K.L. Characteristics of very poor outcome schizophrenia. *American Journal of Psychiatry*, 144:889-895, 1987.
- Lohr, J.B., and Bracha, H.S. Can schizophrenia be related to prenatal exposure to alcohol? Some speculations. *Schizophrenia Bulletin*, 15:595-603, 1989.
- Losonczy, M.F.; Song, I.S.; Mohs, R.C.; Small, N.A.; Davidson, M.; Johns, C.A.; and Davis, K.L. Correlates of lateral ventricular size in chronic schizophrenia, I: Behavioral and treatment response measures. *American Journal of Psychiatry*, 143:976-981, 1986.
- Mednick, S.A.; Machon, R.A.; Huttenen, M.O.; and Bonett, D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry*, 45:189-192, 1988.
- Nowakowski, R.S. Basic concepts of CNS development. *Child Development*, 58:568-595, 1987.
- Suddath, R.L.; Cristison, G.W.; Torrey, E.F.; Casanova, M.F.; and Weinberger, D.R. Cerebral anatomical abnormalities in monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, 322:12:789-794, 1990.

Acknowledgment

This research was supported in part by NIMH Award R29 MH-43537 to H.S. Bracha, M.D.

H. Stefan Bracha, M.D.
Associate Professor of
Psychiatry and Neurology
Division of Developmental
Psychopathology
University of Arkansas for
Medical Sciences and
Director, Neuropsychiatric
Evaluation Unit Psychiatry Service
Veterans Affairs Medical Center
North Little Rock, AR 72114-1706

Sluggish Schizophrenia

To the Editors:

In 1989, the *Schizophrenia Bulletin* (Vol. 14, No. 4 and an appendix) published an exchange of information between Soviet and United States psychiatrists on the diagnosis of schizophrenia. I submitted an article to the *Bulletin* dealing with problems with the articles included in that issue but the reviewers of my article felt that the matter had already been well covered. The issue

concerned the presentation of information in the *Bulletin* that I believe to be linked with the abuse of psychiatry in the U.S.S.R. I should be grateful if you would make known to your readers the fact that a commentary on this subject is available from me as a critique on sluggish schizophrenia, published in the *Bulletin of the Departments of Education & Research of London Psychiatric Hospital* (Vol. 5, No. 1, 1991).

H. Merskey, D.M.
Professor of Psychiatry
University of Western Ontario
London Psychiatric Hospital
London, Ontario, Canada

An Invitation to Readers

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, labora-

tory, or community, and to share ideas—including those that might seem to be radical notions. We welcome all comments.—*The Editors.*

Send your remarks to:

At Issue
Research Publications and
Operations Center
National Institute of Mental Health
Alcohol, Drug Abuse, and Mental
Health Administration
5600 Fishers Lane, Rm. 10C-16
Rockville, MD 20857