Anatomy of Schizophrenia Revisited

by Janice R. Stevens

Abstract

The search for an anatomy of schizophrenia has engendered an enormous, almost indigestible mass of data. In no studies do all patients show the same deviations from control samples. No morphological or microscopic abnormality has been found that is either necessary or sufficient for the diagnosis. In contrast to epilepsy, in which a proliferation of excitatory pathways or inadequate inhibitory factors are paramount, schizophrenia may represent a genetically and age-determined elaboration of one or more inhibitory networks in response to specific physiological events (e.g., the increased neuronal activity in limbic and hypothalamic structures during the physiological events of puberty) or to brain injury or defect. Current diagnostic classifications, including the positive-negative categories, have not led to separation of the disorder into etiologically or pathologically similar subgroups. Analysis of morphological and other biological pathology by a different nosological principle, such as trajectory of the illness, and separate correlation of anatomical and other biological outliers with clinical and demographic factors may be more successful strategies than pooling and averaging results from a mixture of patients diagnosed with schizophrenia.


The introduction of increasingly specific criteria for the diagnosis of schizophrenia has improved the reliability of interrater diagnosis, but has not greatly decreased the variability of morphological, pathological, and neurochemical changes reported among various studies and within the same study of patients with this diagnosis. In fact, using current diagnostic criteria, the larger the sample studied, the greater is the variability in the anatomical findings and the greater the overlap with controls (Chua and McKenna 1995). Ventricular enlargement, diffuse or focal neocortical atrophy, smaller size of mesial temporal structures or specific subcortical nuclei, and a host of unusual histological findings have been reported in the brains of varying numbers of patients diagnosed with schizophrenia. None of these findings is, however, ubiquitous in, necessary or restricted to, or sufficient for the diagnosis of schizophrenia. This suggests that schizophrenia may be, like epilepsy, a response to a number of different causes, only certain types of which are associated with specific morphological or other pathological changes. DSM-IV (American Psychiatric Association 1994), ICD-10 (World Health Organization 1994), and positive-negative classification systems have not succeeded in sorting out these different pathologies (Carpenter and Kirkpatrick 1988).

The articles in this issue provide an impressive background for considering what anatomical changes, if any, are either associated with or are likely to explain a biological basis of schizophrenia. In this article, I propose two new strategies to disaggregate some of the reported clinical and morphological findings:

1. Decursus morbi (clinical course, trajectory): Examine morphologic and other biologic data after dividing patients diagnosed with schizophrenia by the clinical course of the illness, instead of pooling data from large numbers of patients diagnosed with schizophrenia by current classifications or by traditional subtypes. This approach may avoid some of the overlap of morphologic and other biologic measures present in comparisons of pooled average data from schizophrenia patients with different courses and thus perhaps etiology.

2. Evaluation of outliers: Instead of comparing averages of pooled morphologic or histologic features from cohorts of schizophrenia patients with those of matched controls, patients with the largest deviation (e.g., > 1 standard deviation [SD]) from the control mean for each mor-

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phologic (or other pathologic) finding should be compared with respect to clinical and demographic data with schizophrenia patients whose findings fall within 0.5 SD or less of the control mean and with similar data from matched normal controls.

**Decursus Morbi**

There are three principal trajectories for a schizophrenic illness: (1) a single attack with more or less total recovery, (2) repeated attacks with moderate but not total recovery, and (3) a progressive course to chronic debility. Each of these three scenarios resembles the course of a number of infectious, neurodestructive, autoimmune, genetic, and metabolic disorders. Meaningful analysis of the neuro-pathology and neuroanatomy of schizophrenia may be facilitated by a multivariate analysis that assesses the contribution of each anatomical, clinical, and demographic variable to the probability of being a trajectory 1, 2, or 3 schizophrenia. These variables can include measures of ventricles; volume of cortex, frontal and temporal lobes, hippocampus, and subcortical nuclei; specific receptor, molecular, and biochemical factors; gender; ethnicity, age and type of onset; premorbid history including IQ, family history, medical history, and obstetric and prenatal factors; timing and degree of cognitive impairment; specific clinical signs and symptoms; and any other clinical, demographic, biochemical, or anatomical variables deemed pertinent.

We may then consider whether one or more of these trajectories best fit the usual course of neurodevelopmental, genetic, or neurodestructive-neurodegenerative (including infectious) disorders.

**Neurodevelopmental Disorders.** The common neurodevelopmental disorders that affect cerebral and mental development are mental retardation, attention deficit disorder, cerebral palsy, and specific disorders of speech, reading, arithmetic, motor abilities, and social behavior. The underlying causes may be, but are not always, found in the morphology of the brain (microcephaly, hydrocephaly, neural migration defects, microgyria, lissencephaly, absence of normal asymmetry or symmetry of specific brain regions) or in specific histological and biochemical abnormalities. Neurodevelopmental disorders are generally manifest in the first 10 years of life by delayed motor or mental milestones or disturbances of movement, posture, and behavior. These signs and symptoms rarely progress and may improve with treatment and with time. In Huber's (1957) and Gross and Huber's (1995) study of the trajectory of illness in nearly 500 adults with schizophrenia, only 11 percent had a history of pronounced behavioral abnormality before onset of the illness. Gittleman-Klein and Klein (1969) reported premorbid abnormalities in approximately one-third of subjects who were diagnosed later with schizophrenia. The distribution of abnormalities was clearly bimodal. Thus, although the presence of abnormal behavior in childhood must be considered a risk factor, premorbid behavior or personality disturbance is neither necessary nor sufficient for the development of schizophrenia. Moreover, the course of most neurodevelopmental disorders differs dramatically from the three most common courses for schizophrenia noted above. For further understanding of the role of neurodevelopmental features, it will be useful to determine which, if any, of the three major trajectories of illness cited above are associated most commonly with a history of significant childhood motor, social, or mental disabilities. Neurodevelopmental disorders should be distinguished from perinatal insults, such as brain ischemia and hemorrhage, and from infections or injuries in infancy and childhood, the sequelae of which may mimic neurodevelopmental disorders.

**Genetic Disorders.** Genetic disorders, including the inborn errors of metabolism, such as phenylketonuria or the lipodystrophies, may be expressed in the early years of life or delayed until adolescence or adulthood. After onset, seizures, behavior disorders, psychoses, and mental dilapidation may or may not develop in the disorders that predominantly affect gray matter. Disturbances of posture, movement, sensation, and intellect are more prominent for disorders that preferentially affect the white matter of the brain. The clinical course of many schizophrenias is compatible with the typical course of many genetic disorders. However, the fact that total or nearly total spontaneous recovery occurs in one-third to one-half of the individuals who are diagnosed with schizophrenia would be unusual for a majority of genetic disorders of the nervous system. Only 30 to 45 percent of monozygotic twins with schizophrenia have an affected cotwin, and additional precipitating or predisposing factors have been sought to explain this discordance (Torrey et al. 1994). In this aspect, schizophrenia resembles epilepsy, a syndrome with an equally common positive family history, but with contributory factors, many of them similar to those often cited for schizophrenia (e.g., perinatal insult and infection), that are also frequent and appear to be additional risk factors, rather than alternatives to hereditary predisposition.

**Neurodegenerative and Neurodestructive Disorders.** The majority of these disorders are remarkable because they occur in individuals previously deemed well. Their onset may be sudden as in cerebrovascular accidents,
multiple sclerosis, and specific infectious encephalitides or insidious as in Huntington’s chorea, Parkinsonism, Alzheimer’s disease, and several infectious encephalopathies (Creutzfeldt-Jakob disease and AIDS). Neurodegenerative and neurodestructive disorders may progress over a few days, months, or years or may demonstrate exacerbations, remissions, and formes frustes that allow return of the affected individual to premorbid status. This model best fits the trajectories of a majority of individuals diagnosed with schizophrenia, more than half of whom have no apparent antecedent cause or family history of this illness, one-third to one-half of whom recover, and equal numbers of whom follow a remitting-exacerbating or progressively worsening course during the first months or years of the illness with varying degrees of permanent cognitive and affective disability (M. Bleuler 1978; Ciompi 1980; Huber et al. 1980; Watt et al. 1983; Harding 1988).

In a review of 532 hospitalized patients meeting the St. Louis criteria for schizophrenia, Johnstone (1992) reported that, over a 10-year period, both occupational status and IQ significantly declined from premorbid status in over half of the patients. This study provides evidence for social and cognitive decline over the initial 5 to 10 years of the illness in varying percentages of schizophrenia patients, as initially reported by Bleuler (1911/1950) and Kraepelin (1919/1971) and more recently documented by Bilder et al. (1992), Fenton and McGlashan (1994), and Waddington et al. (1995). The evidence that schizophrenia is frequently a progressive disabling illness has been challenged by some investigators who are studying current, neuroleptic-treated schizophrenia. Averaging together data from neuroimaging or neuropathological studies of large numbers of cases of diverse course by using classic subgroups according to DSM and ICD that seem to be irrelevant to either course or etiology may obscure important relationships in the search for pathology of the illness.

Most recent data concerning the clinical course of schizophrenia reflect changes caused by neuroleptic treatment. Neuroleptics may also change the neuropathology by ameliorating or arresting the disease progress (Huber et al. 1980; Crow et al. 1986; Wyatt 1991), enlarging the lenticular nuclei (Heckers et al. 1991; Jernigan et al. 1991), and causing tardive dyskinesia.

Evaluation of Outliers

My second suggestion for disaggregation of pathological and morphological changes in schizophrenia is to select outliers, cases that present deviations of more than 1 to 2 SDs from the control mean for morphologic (or histologic and biochomic) measures. Clinical and other features of these biologic outliers should be compared with similar measures from patients with the same diagnosis but whose morphologic (or histologic or biochemical) measures fall within 0.5 SDs of the control mean and with matched normal controls. This outlier approach, by selecting for only definite pathology, has been valuable for unraveling the pathophysiology of other heterogeneous disorders, but has only occasionally been employed in studies of brain morphology (e.g., Williams et al. 1985; Kanba et al. 1987) or other biologic factors in schizophrenia.

Where Is the Pathology?

In an earlier article, “An Anatomy of Schizophrenia” (Stevens 1973), I noted the remarkable similarity of many perceptual disturbances of schizophrenia to the auras of patients with mesial temporal epilepsy. The important difference is that the individual with schizophrenia considers these aberrant percepts to be “real,” whereas in epilepsy they are recognized as alien, as auras. Amelioration of these symptoms by neuroleptics suggested that the pathology of schizophrenia might be located in a dopamine-biased gate “downstream” from mesial temporal structures. This hypothesis ignored, however, the defect symptoms and signs such as reduced concentration, attention, and motivation, which often antedate the psychosis and are more likely to be associated with pathology in cortical association areas and/or brain regions responsible for focused attention. Those brain regions include the midline thalamic nuclei and other structures that surround the third and lateral ventricles, including the major pathways between limbic system, hypothalamus, thalamus, basal ganglia, and neocortex. The temporal sequence of events in the history of most schizophrenias suggests that disturbances in attention, perception, and affect precede the onset of frank psychotic symptoms (Chapman 1966; Huber et al. 1980; Häfner 1993) and may thus set the stage for the subsequent emergence of the positive symptoms of delusions and hallucinations. Positive symptoms may be released in the Jacksonian sense (Jackson 1873/1958) or emerge secondary to a pathological restitution process, such as compensatory aberrant reinnervation (Stevens 1992).

Morphological Changes: Enlargement of the Cerebral Ventricles

The most widely replicated pathological anatomical finding in both postmortem and neuroimaging studies of schizophrenia is the increased volume of the lateral and
third ventricles in 15 to 30 percent of patients compared with controls (Southard 1914, 1915; Jacobi and Winkler 1927; Huber 1957; Haug 1962; Johnstone et al. 1976). Among monozygotic twins who are discordant for schizophrenia, ventricular volume was larger in the affected cotwin (Reveley et al. 1981; Suddath et al. 1989). In studies in which the size of the third ventricle was measured, it was reportedly the first to enlarge or was enlarged out of proportion to the lateral ventricles (Huber 1957; Dewan et al. 1983; Weinberger 1984; Kanba et al. 1987; Iacono et al. 1988; Raz and Raz 1990; Chua and McKenna 1995) and was even demonstrated by echoencephalography before the earliest computed tomography reports (Shütter et al. 1974).

Ventricular enlargement is not unique to, necessary, or sufficient for the diagnosis of schizophrenia. Its importance is that, unless head size differs from normal, as it generally does not in schizophrenia (Kanba et al. 1987; Pearlson et al. 1991), ventricular enlargement means that brain tissue has been lost after completion of growth of the cranium. The source of this tissue loss has been sought by correlating ventricular volume with several anatomical measures and clinical factors. No correlations were found between ventricular enlargement and cortical or medial temporal atrophy (Daniel et al. 1991; DeLisi et al. 1995), obstetical complications, premorbid social function, genetic factors, duration of illness, or age at onset (Done et al. 1991; Jones et al. 1994; Lim et al. 1996). Poorer outcome and negative family history for schizophrenia were associated with enlarged third and lateral ventricles in some but not all reports (Gross et al. 1982; Williams et al. 1985).

Ventricular enlargement occurs in a wide variety of neurodevelopmental, genetic, and neurodestructive (especially subcortical) disorders and is also reported in varying percentages of individuals with affective disorders (Gross et al. 1982; Andreasen et al. 1990). Studies of patients in different stages of schizophrenia generally report that the ventricles are larger in chronic schizophrenia than early in the illness (Raz and Raz 1990). This finding could signify progressive tissue loss during the illness or could represent greater severity of the initial causal factor(s). Although several studies report progressive increase in ventricular size in a cohort over time (Huber 1957; Haug 1962; Iacono et al. 1988; Kemali et al. 1989; Woods et al. 1990), others do not (Ilowsky et al. 1988; Vita et al. 1988; DeGreef et al. 1991; Jaskiw et al. 1994; DeLisi et al. 1995). Failure of many studies to find progressive ventricular enlargement in averaged data from the majority of patients has contributed significantly to the revival of neurodevelopmental hypotheses (Murray and Lewis 1987; Weinberger 1987). However, examination of individual cases even in these studies shows that, although the volume of ventricles did not increase over time for averaged group data, enlargement did occur in a small percentage of individuals in each study. This finding reflects both heterogeneity and the fact that most initial imaging studies have been done months or years after onset of the earliest symptoms of schizophrenia (Loebel et al. 1992). If defect symptoms precede productive (positive) symptoms and first hospitalization by months or years in a majority of patients, as reported by many investigators (Chapman 1966; Huber et al. 1980; Hafner 1993), the initial imaging study at first hospitalization may miss the period in which brain tissue is lost and the ventricles enlarge. The onset of psychosis may then be seen as an aberrant response to damage or defect similar to the seizures of epilepsy or the confabulations of Korsakoff psychosis.

Which Brain Structures Are Responsible for Expansion of the Ventricular Space and When Did It Happen?

Cortical Atrophy. Cortical atrophy which is sometimes diffuse but is more often confined to frontal or temporal gyri, has been described in 5 to 15 percent of people with schizophrenia both from postmortem material and from cerebral imaging by some but not all investigators. When present, cortical atrophy was not correlated with ventricular enlargement (Daniel et al. 1991) or with the characteristic pathological changes of Alzheimer’s disease or vascular dementias, even in demented schizophrenia patients (Arnold et al. 1996). Although interpreted as a neurodevelopmental anomaly by Lim et al. (1996), significant loss of cortical or mesial temporal tissue, if developmental, should result in decreased cranial volume and head size if the responsible events occurred before full brain growth is reached at 10 to 11 years. Yet, brain and cranial volume of a majority of schizophrenia subjects are similar to controls (Kanba et al. 1987; Grove et al. 1991; Pearlson et al. 1991), particularly when socioeconomic factors are controlled (Andreasen et al. 1990; Jones et al. 1994; Zipurksy et al. 1994). As with ventricular enlargement, pooling data from specimens of diverse etiology and pathology may obscure evidence of cause in individual cases of cortical atrophy or of small brains or heads that, when pooled with the majority, shift the overall average to the left in some studies.

Atrophy, Dystrophy, or Dysplasia of Medial Temporal and Subcortical Structures. Bogerts et al. (1985) were the first to report diminished size of hippocampus, amygdala, globus pallidus, and periventricular gray and
entorhinal cortex in a percentage of brains of schizophrenia patients. Smaller medial temporal structures were subsequently reported in some but not all imaging studies and not by the neuropathological study of Heckers et al. (1990). Before the Bogerts et al. (1985) report, pathology in these medial temporal structures was predicted from analysis of the mainly productive or positive symptoms of the disorder (Stevens 1973; Torrey and Peterson 1974). However, it should be noted that Bogerts et al. (1985) demonstrated diminished size of hippocampus or amygdala at least 1 SD from the mean in only 7 of their 13 brains with schizophrenia (figure 1). Cytoarchitectural changes (Jakob and Beckmann 1986; Kovelman and Scheibel 1986), neuron loss, and other histological findings reported in mesial temporal structures in a percentage of brains of schizophrenia subjects are reviewed and critiqued by Dwork (1997, this issue).

Much more severe pathology in the mesial temporal region, including severe neuron loss and gliosis found in many patients with temporal lobe epilepsy, or even total surgical removal of the amygdala, hippocampus, and anterior third of the medial temporal lobe is not often associated with schizophrenia. Something else must happen to these individuals with mild or modest medial temporal atrophy or dystrophy to cause schizophrenia. Although principal suspects have been the frontal lobes, macroscopic and microscopic examination of this region has given few or contradictory results (Benes et al. 1986; Pakkenberg 1993; Selemon et al. 1995; reviewed by Heckers 1997, this issue). Other regions that may relate to the significant attentional impairment so common in schizophrenia are the subcortical structures proximate to the enlarged third and lateral ventricles. Histological, molecular, and ultrastructural features in the medial thalamic nuclei, hypothalamus, fornix, ascending reticular system, medial forebrain bundle, and other structures proximate to the third ventricle have been insufficiently examined with modern quantitative neuropathological and molecular techniques.

Gliosis. After birth, the brain responds to tissue loss by forming glial scars. The current popularity of a neurodevelopmental hypothesis of etiology rests in part on the failure of several recent histological studies to find a significant increase in gliosis, the hallmark of postnatal brain injury or inflammation, in averaged material from cerebral cortex of schizophrenia subjects (Benes et al. 1986; Selemon et al. 1995). However, there are several reports of gliosis, especially in subcortical and periventricular areas, in brains from varying percentages of patients diagnosed with schizophrenia. These reports include not only qualitative results (Winkelman and Book 1949; Nieto and Escobar 1972; Fisman 1975; Stevens 1982; Bruton et al. 1990), but also quantitative studies (Blinkov and Glezer 1968; Falkai et al. 1991; Arnold et al. 1996). Although Roberts et al. (1986) found no statistical difference in averaged density of glial fibrillary acid protein (GFAP) staining in a comparison of subcortical and cortical regions of pooled schizophrenia and control brains, densitometry readings were higher in the schizophrenia brains in every region studied especially in subcortical areas. Unfortunately, individual differences were not reported, and a significant increase of GFAP in specific individuals may have washed out in the averaging process. GFAP is a measure of active proliferation of astrocytes as occurs in ongoing disorders, such as Huntington’s chorea or Alzheimer’s disease, and may not be revealed by GFAP staining if neuron loss occurred many years before death (Stevens et al. 1992; Eng and Ghirnikar 1994). Other acute or subacute degenerative changes are absent in brains of schizophrenia patients, suggesting that if a prior destructive event has occurred, it is not continuing at the time of death, has been arrested by treatment, or is a slow and indolent process that provokes no glial response (e.g., apoptosis). Averaging data from pooled samples obscures individual pathology that may correlate with specific clinical variables, such as course and duration of illness, type of onset, and family history.

Schizophrenia and Epilepsy: Alternative Genetically Determined Brain Responses to a Variety of Predisposing Factors?

Analysis of the course of the syndrome and of biological outliers has been useful for disaggregating the multiple types and etiologies of epilepsy. Epilepsy was formerly considered to be a homogeneous disease but is now acknowledged to be a symptom of a wide variety of morphological, physiological, or molecular abnormalities. As in schizophrenia, lateral ventricle enlargement is present in a minority of patients, and more than half of all brains examined from patients with epilepsy present no specific pathological features. Hippocampal neuron loss and hippocampal sclerosis (gliosis) were first described in patients with generalized epilepsy and are present in 40 to 50 percent of all patients with temporal lobe epilepsy. Posttraumatic scars and developmental or neoplastic changes are found in 10 to 15 percent of brains from individuals with various focal or generalized seizure disorders and often relate anatomically to the type of seizure. Functional imaging discloses hypometabolism in symptom-related areas of focal epilepsy in the interictal period.
Figure 1. The difference from normal size of several subcortical structures in 13 individual brains with schizophrenia

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Squares with single hatching: > 1 standard deviation (SD) below control mean; cross-hatching: > 2 SDs below control mean; solid shading: > 3 SDs below control mean; * > 1 SD above control mean; ** > 2 SDs above control mean; *** > 3 SDs above control mean; N: within 1 SD of control mean; - No data. Note that there was significant deviation from control mean in six of nine brains in which amygdala-hippocampus (AMYG, HIP) could be measured, six of seven for parahippocampal gyrus (PHG), six of nine for external pallidum (EXT PALL); in five of nine for periventricular grey (PVG), and four of eight for putamen, etc. A decrease of 3 SDs from the mean was shown for bed nucleus of stria terminals (BNST) in one case and of hippocampus in one case. Clinical phenomenology (right-hand column) showed only modest correlations with size deviations of individual nuclei. NACC = nucleus accumbens; CN = caudate nucleus; PUT = putamen; STRI = striatum; INT PALL = internal pallidum; INF Horn = inferior horn of lateral ventricle. Data from Bogerts et al. 1985; reproduced with permission from Stevens 1986.

and hypermetabolism in these areas during the seizure (Engel et al. 1982).

In schizophrenia, lateral and third ventricle enlargement is also reported in a minority of patients. The volume of the hippocampus is reduced in some brains of schizophrenia patients, but this reduction is not, as in epilepsy, frequency associated with marked neuronal loss, dysplasia, severe gliosis, or anomalous proliferation of
Clinical correlations related to decreased volume of several structures have been explored only tentatively, and these studies have demonstrated the considerable variability of each morphological finding (Stevens 1986; see figure 1). Imaging studies have reported decreased temporal lobe, frontal lobe, whole brain, or cerebral cortex volume from some averaged samples, but not others. There is considerable variability and up to 90 percent overlap with controls. In contrast to epilepsy, in which an electroencephalogram (EEG) is often diagnostic, the EEGs of schizophrenia subjects are generally normal or only mildly abnormal and without specific or localizing features.

In further contrast to epilepsy, in which functional imaging and EEG often identify the epileptic focus, functional imaging of the brain (positron emission tomography or magnetic resonance imaging) in schizophrenia subjects has demonstrated hypofrontality in some but not all studies of patients at rest. In contrast to normals, who activate contralateral motor cortex uniquely during a simple manual task, abnormal activation of many brain areas bilaterally was reported during performance of the same task by some schizophrenia patients (figure 2). This striking observation suggests that, instead of an unstable balance of ictal hyperexcitability and interictal hypoexcitability as in epilepsy, in schizophrenia the brain is associated with inappropriate inhibition of specific brain areas and aberrant activation of others during even a simple motor task.

Axonal sprouting in dentate gyrus in epilepsy seems to represent an aberrant response of glutamatergic granule cells to excitotoxic or anoxic brain injury (Sutula et al. 1992). Schizophrenia may instead represent a genetically determined compensatory proliferative response of axons, dendrites, or receptors in other (nonglutamate) systems in response to diverse brain insults. The favorable effect of specific neuroleptic agents in individuals cases and the psychotogenic properties of excitatory antagonists (e.g., amphetamines, MK801, and phencyclidine) suggest that, instead of an excess of excitatory elements or decrease in inhibition as in epilepsy, in schizophrenia the brain responds to precipitating events or to brain injury by excessive elaboration of one or more components of cerebral inhibitory networks (e.g., monoamine, gamma-aminobutyric acid, endogenous excitatory antagonists). The type of the brain response depends on the nature of the precipitant; the age of occurrence; and individual genetic factors that regulate neuronal death, glial response, and axonal and dendritic expansion or repair. These factors are likely to play important roles in both schizophrenia and epilepsy.

References


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**In Memoriam**

The field of schizophrenia research lost one of its great, creative and energetic investigators with the untimely death of Michael J. Goldstein, Ph.D., who died on March 14, 1997. Dr. Goldstein was Professor of Psychology at the University of California at Los Angeles (UCLA), Chief of the Family Assessment and Treatment Laboratory at the UCLA Clinical Research Center for Schizophrenia and Psychiatric Rehabilitation and a long-standing member of the Editorial Board of *Schizophrenia Bulletin*. Despite Dr. Goldstein’s battle with prostate cancer, he remained active and productive with research and teaching activities to the very end.

At the time of his death, he was principal Investigator of a MERIT NIMH grant, "Behavioral Family Therapy & Lithium for Bipolar Disorder" and Director of the Research Training Program in Schizophrenia for pre- and post-doctoral trainees. Dr. Goldstein had an international reputation as a leader in the area of psychosocial research of major psychiatric disorders, wrote a much-used textbook in Abnormal Psychology, and had research collaborators all over the globe. He was a revered teacher of undergraduates, graduate students, and postdoctoral trainees, and won the prestigious UCLA Distinguished Teaching Award. To the end of his life, he was doing what he did best; namely, mentoring a new generation of schizophrenia researchers and supervising five doctoral dissertations.

Dr. Goldstein was born in New York City and was educated at Iowa State University, Washington State University, and the University of Washington where he received his doctorate in clinical psychology in 1957. In the following year, he began his enormously successful career at UCLA, rising through the ranks to full professor in 1969. He was the recipient of numerous awards and honors, including a Fulbright Research Professorship at the University of Copenhagen, a Visiting Professorship at the University of Amsterdam, and Awards from the American Psychological Association. He also served as President of the Society for Research in Psychopathology.

In the 1970s, Dr. Goldstein directed the first treatment research study that documented the efficacy of structured and educational forms of family intervention in schizophrenia. Supplementing standard doses of fluphenazine decanoate with 6 weeks of family intervention resulted in zero relapse rates over the 6-month follow-up period. Medication alone or low doses of medication supplemented by family intervention were significantly less effective in forestalling relapse. This study inspired an era of research on family psychoeducation and behavioral family management interventions in schizophrenia that have replicated Dr. Goldstein’s original, favorable findings in the United States and internationally. Dr. Goldstein was also interested in the interactional nature of expressed emotion and recently demonstrated that subclinical psychopathology exhibited by a person with schizophrenia appears to evoke criticism, thereby contributing to high expressed emotion and greater liability to relapse.

Author of over 200 publications, Dr. Goldstein was a Fellow of the American College of Neuropsychopharmacology, the Society for Research in Psychopathology, the American Psychological Association, and a Councilor of the Association of Clinical Psychosocial Research. He recently received the Distinguished Contribution Award of the Society for the Science of Clinical Psychology and the Gerald Klerman Award of the Association for Clinical Psychosocial Research. He is survived by his loving wife and "partner," Vida Goldstein, two daughters, a son, and three grandchildren. He will be missed by all those who were touched by his personal warmth, generous teaching and consultation, and professional wisdom.

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