Schizophrenia Research in the Intramural Research Program, National Institute of Mental Health: Editor’s Introduction

by Richard Jed Wyatt

Abstract

One of the major reasons for the existence of National Institute of Mental Health’s Intramural Research Program is the study of schizophrenia. The program provides relatively stable funding for the long-term examination of the basic and clinical sciences as they relate to this major public-health problem. This article and those that follow review some of the past and current contributions to our understanding of schizophrenia that have emanated from the Intramural Research Program.

This edition of the Schizophrenia Bulletin surveys the wide-ranging topics being examined by investigators within the National Institute of Mental Health (NIMH) Intramural Research Program. The principal interest of the Program in investigating the causes, treatment, and potential cure for or prevention of the major neuropsychiatric disorders—schizophrenia and affective disorders—is longstanding and the reason for its existence.

Initial Efforts

The Program’s early history was described most eloquently by Dr. Robert A. Cohen (1984), a former Associate Director. The early years saw a mixture of psychosocial and biological research. Wynne and Singer, for example, found what they termed “communication deviance” in families with schizophrenic individuals. While today we do not believe that communication deviance is the cause of the disorder, whether the altered communication among family members is a product of having a disturbed individual in the family or precedes the illness is still an unresolved chicken-and-egg dilemma.

Another chicken-egg problem developed when several studies observed that a disproportionately high ratio of people in large urban areas were hospitalized for schizophrenia. A hypothesis evolved that this setting contributed to the development of the illness. It held that urban life allowed for greater social isolation; in response, some individuals became schizophrenic because they failed to develop conventional coping strategies. On the other hand, the social isolation of the schizophrenic individual could just as well have been present because it was part of the disorder. Data from work by Clausen and Kohn of the Program’s Laboratory of Socioenvironmental Studies indicate that social isolation per se did not produce schizophrenia.

Other work involved the study by Rosenthal of the Genain Quadruplets (“schizophrenic” identical quadruplets with varying forms and severity of psychopathology). In this and in subsequent adoption studies done with Wender and Kety, Rosenthal demonstrated that some aspect of the disorder is genetically transmitted. (Kety describes some of his more recent adoption research in this issue.)

Cohen’s history notes the Program’s most celebrated discovery: the enzyme catechol-O-methyltransferase, for which Julius Axelrod received the 1970 Nobel Prize in Medicine. This discovery focused attention on synaptic mechanisms involved in monoaminergic neurotransmission. The field of central nervous system synaptology was born; a treatment for Parkinson’s...
disease was found; and major investigations of monoamine metabolism in the schizophrenias and affective disorders were initiated.

In this issue, Mirsky reviews the productive history of one of the oldest laboratories in the Program, the Laboratory of Psychology and Psychopathology (previously the Laboratory of Psychology). Early on, David Shakow, founder of the laboratory, described the reaction time deficit of individuals with schizophrenia, leading to his hypothesis that schizophrenic patients were unable to achieve a “major set.” Having a “major set” included appropriate attention and sensory adjustments to receive outside stimulation. It included disregarding irrelevant sensations while being open to hypothetical situations. Schizophrenic individuals, Shakow demonstrated, were able to achieve only a “segmental set.” Their preparation for a stimulus was flawed, for they considered only a minor part of the whole stimulus. He concluded that schizophrenic individuals cannot place the stimulus into an appropriate context.

Mirsky then describes work begun several years ago (and still under way). He highlights the Israeli High-Risk Study (begun by Rosenthal), which showed that children of schizophrenic parents, when professionally raised on a kibbutz, had twice the incidence of schizophrenia when professionally raised on a kibbutz, had twice the incidence of schizophrenia. Although the offspring of schizophrenic parents do not have a particularly high incidence of affective disorders, in general, the children in this study tended to have affective disorders. No explanation for this discrepancy currently exists. Mirsky further discusses the various components of attention that are altered in schizophrenia; he tentatively concludes that the locus of abnormality is spread throughout the brain. The attentional system appears to be, therefore, more vulnerable to damage, and possibly also more likely to compensate than if it were discretely located.

**Current Efforts**

Following Mirsky’s article are articles describing neuropathology and adoption studies, hypothesized pathophysiology, etiologies, treatments, and outcomes. Weinberger and Berman review a series of studies using regional cerebral blood flow and positron emission tomography (PET) to describe abnormalities in the prefrontal cortex of schizophrenic individuals. Because this area of cortex appears to be responsible for certain forms of abstract reasoning, its dysfunction could have considerable importance to our understanding of schizophrenia. Weinberger and Berman also discuss possible reasons why some studies find prefrontal hypometabolism and others do not. They point out that studies in which schizophrenic patients have been given tasks that activate the prefrontal cortex are more likely to demonstrate abnormalities. Specific tasks are capable of locking the brain into a prescribed activity that is standardized across subjects and, when a limited part of the brain is stressed, can bring out weaknesses that otherwise might not be apparent.

In disorders with known frontal-lobe neuropathology, such as Alzheimer’s and Pick’s disease, decreased frontal blood flow is found in both the resting and activated (stressed) state. From their studies showing hypofrontality only under “task” conditions, Weinberger and Berman propose that the lesion of schizophrenia is not intrinsic to the frontal cortex. Rather, the lesion or lesions rest outside it. The extracortical damage, they suggest, might be in the ascending dopaminergic projections to the cortex. They point out that dopaminergic hypofunction at the cortical level has been reported to cause subcortical dopaminergic hyperfunction in the rat. In this model, hypofunctioning of dopamine to the prefrontal cortex would produce hyperfunctioning subcortical dopamine. There could be simultaneous deficit (cortical hypofunctioning) and productive (subcortical hyperfunction) symptoms from one lesion.

Robert M. Cohen and his colleagues used 18F-2-fluoro-2-deoxy-D-glucose PET to study the metabolic rate in both schizophrenic patients and controls during a directed-attention test. Normal individuals performing a task requiring auditory discrimination had increased middle prefrontal cortex metabolic activity associated with accurate performance. No such association was present in the schizophrenic patients, even when they performed well. The lower metabolic rates were present in both the right and left prefrontal cortex. Patients given neuroleptic medications were similar to controls in their responses. There was a strong association between activity in the middle prefrontal region and performance. Early data indicate that similar abnormalities may occur in individuals with manic-depressive illness. This is extremely important because it could indicate that the ab-
normalities are related to some aspect of being psychotic rather than to a specific disorder.

Goldberg and Weinberger describe their effort at using neuropsychological tests to help determine where specific nervous system alterations occur in schizophrenia. They found that acutely psychotic adolescents, almost all hospitalized for the first time, do significantly less well on the Performance subscale of the Wechsler Intelligence Scale for Children (Revised) than on the Verbal subscale. The same pattern is also found in chronically ill schizophrenic adults. The acutely ill adolescents had lower Full-Scale IQs than an appropriate control group. These investigators suggest that their data are consistent with data from computed tomography indicating that the neuro-pathological changes in schizophrenia are not progressive. Further, Weinberger has hypothesized that schizophrenia is a developmental disorder; i.e., the future schizophrenic individual grows into an altered brain. Early in life, the abnormality is not evident because the affected functions of the brain have not yet been required. It is only when those regions “come online” that the schizophrenia is manifest.

Several neuropsychological tests can be given to locate the area of the brain that is altered. Schizophrenic individuals are known to do poorly—even when given detailed instructions—on the Wisconsin Card Sorting Test, a test that measures frontal lobe function. The same patients do well with memory and other tasks felt to have less specificity for the frontal lobe.

Other areas of the brain have also been examined. DeLisi et al. studied perinatal complications in families having more than one child diagnosed with schizophrenia. Schizophrenic siblings had twice the percentage of perinatal complications as nonschizophrenic siblings. A high incidence of perinatal complications in schizophrenia has been reported in previous NIMH studies. In the DeLisi et al. study, schizophrenic individuals had smaller medial temporal lobes as seen on magnetic resonance imaging (MRI). There appeared to be no association, however, between perinatal complications and the MRI findings.

Karson et al. measured voltage of several frequencies (power spectrum analysis) of a multilead electroencephalography (EEG). They were careful to eliminate electrical artifacts from eye blink and ocular movements. The group found that medication-free, chronic schizophrenic patients have increased EEG slowing (delta activity) over the entire cerebral cortex. There was reduced (<10.2 Hz) alpha frequency in those patients with increased ventricular size.

Duncan studied the P300 (a late positive voltage) component of event-related brain potentials. She, like others, found it to be smaller in schizophrenic individuals. Duncan has taken this finding further, however, and found that when schizophrenic patients are placed on neuroleptics, the P300 component of a visual stimulus approaches normal. The P300 to an auditory stimulus does not change; it remains low. The auditory P300 abnormality appears to be more a trait marker; perhaps it is related to a core deficit of processing auditory information in schizophrenic individuals.

Zahn summarizes his work on autonomic psychophysiology and places it in perspective with other work. In general, high sympathetic arousal and slow habituation are associated with acutely ill, unmedicated patients.

Kleinman et al. review the neuropathology of schizophrenia. Although traditional neuropathology has failed to find a pathognomonic lesion in schizophrenia, post-mortem neurochemistry has yielded one of the most replicable findings in schizophrenia research. Increases in dopamine type 2 receptors in the basal ganglia and nucleus accumbens suggest the importance of these structures as well as their afferents and efferents. Kleinman et al. suggest that further studies using new neuropathological techniques (autoradiography, immunocytochemistry, and neural morphometrics) should be used in the study of afferents and efferents to the basal ganglia.

Schizophrenia often occurs in families—but is the clustering in families due to their sharing common genes or a common environment? Kety reviews research efforts in differentiating genetic and environmental contributions to the etiology of schizophrenia. He and his colleagues studied adopted children who later became schizophrenic. Because the schizophrenic adoptees were separated from their parents shortly after birth, they shared little of the same environment with their biological families. The presence of schizophrenia in both the adopted individual and his biological family is likely to be genetic. Initial studies were conducted in Copenhagen; more recently, the rest of Denmark was surveyed, and first-degree relatives...
were interviewed. The larger study confirmed the initial study—an individual biologically related to a schizophrenic individual is more likely to have a schizophrenia-spectrum disorder than someone not related. In addition to giving support for genetic theories of schizophrenia, Kety's studies help improve the diagnoses of schizophrenia and genetically related disorders.

Genetic factors, however important, do not seem to explain schizophrenia in its entirety. Environmental factors, including the possible role of viruses, appear to be necessary. Torrey places the viral hypothesis of schizophrenia in historical perspective. Both Kraepelin and Bleuler noted the possible relationship of infections to schizophrenia; in the 1920's, Menninger was convinced that epidemic encephalitis caused schizophrenia. Renewed interest in possible viral causes of schizophrenia has been fostered by the explosion of information about "slow" and latent neurotropic viruses and their ability to affect cellular systems without necessarily altering morphology. The evidence for viral involvement in schizophrenia is, however, almost entirely circumstantial. The evidence includes observations of an increase in schizophrenic births in the late winter-early spring months, an uneven prevalence worldwide, the description of immunological abnormalities in schizophrenia, and the possible antiviral effects of neuroleptics.

Stevens pursues the viral hypothesis of schizophrenia further by noting the epidemiological similarities between multiple sclerosis and schizophrenia. Both disorders begin in early adult life, have progressive or relapsing courses with increasing disability, and have spontaneous remissions. She suggests that both may be caused by viral infections (acute or persistent), followed by an autoimmune system response. In the immunological model, the virus is not directly responsible for the disorder; it is the body's reaction that produces the damage. The same argument might also be made for the affective disorders.

This view is shared by Pert et al., who begin their paper by reviewing their work in acquired immune deficiency syndrome (AIDS). The AIDS virus envelope gains entry to the host cell by using a specific receptor-attachment sequence (called T[4-8] or peptide T). Having some sequence homology with vasoactive intestinal peptide (VIP), the AIDS virus envelope, which is easily shed, binds to VIP receptors on brain cells. VIP appears to have a neurotropic effect; when VIP's neurotropic effect is blocked by the AIDS virus envelope, this is hypothesized to cause neuronal degeneration and dementia. Pert et al. point out that other viruses, using other receptors, might act like the AIDS virus, but produce schizophrenia. They focus on the influenza viruses. A viral infection of the brain does not necessarily bring severe viral encephalitis. Certain brain cells could be chronically infected. An autoimmune system response could lead the virus to produce damaged cells and disease. The genetic vulnerability to schizophrenia could be the predisposition to produce an autoimmune response to a viral infection.

Merril and Harrington have developed a very powerful technique—two-dimensional electrophoretic protein maps—to look for abnormal proteins in the brain and cerebral spinal fluid (CSF). To date their work has concentrated on the CSF. They have found two unusual proteins in one-third of the schizophrenic patients they examined. The abnormal proteins were also found in patients with other central nervous system diseases, which may be of viral origin, but not in normal controls.

Two-dimensional chromatography as performed by Merril and Harrington is on the forefront of new breed of research, one that uses very powerful separation techniques to determine differences among diagnostic groups. One of the earliest investigators to use such a procedure in psychiatric patients was Linus Pauling. He forced the urine of schizophrenic patients through a 1000-foot-high pressure liquid chromatography column with the idea of comparing the separated products with those from normal urine. This is the empirical approach of the theorectical assayist (Wyatt 1985) who uses techniques to comb through data looking for differences.

Using similar separation techniques, investigators have recently located the general regions on the chromosome where genes for Huntington's disease and a form of bipolar disorder reside. Locating the genetic locus of disease on these chromosomes has occurred without knowing anything about what the genes do. There is a strong expectation that the genes for these disorders will be identified with very little knowledge of their physiological function.

Schizophrenia, however, is a disorder that attracts the theorist. Perhaps the most productive and
dominant hypothesis about the cause of schizophrenia is that schizophrenia is due to an excess of functional brain dopamine—the dopamine hypothesis. Neuroleptics block dopamine receptors and therefore functionally decrease the amount of dopamine available to the receptor. Neuroleptics, however, block the dopamine binding sites in the brain within minutes to hours after administration.

Pickar reminds us that in schizophrenic individuals, neuroleptics take some time to produce their antipsychotic effect. Often their maximum effect is not achieved for several weeks. Pickar stresses the paradox between the pharmacological and the clinical effects of neuroleptics and explores what might be wrong in schizophrenic patients. He has measured the dopamine metabolite homovanillic acid (HVA) in the plasma of schizophrenic patients over time and found a robust correlation between psychosis ratings and HVA concentrations. Unmedicated, acutely psychotic patients initially have a high HVA concentration. With neuroleptic treatment and subsequent clinical response, plasma HVA decreases. The improvement and drop in HVA closely parallel one another. The drop in HVA and the clinical response take several weeks to occur. Pickar's hypothesis is that slowly developing changes in presynaptic dopamine terminals are important to neuroleptic treatment. A possible mechanism is “depolarization block,” by which dopamine neurons decrease their firing rate over time.

Freed proposes a novel hypothesis about the mechanism of action of neuroleptic medications and their therapeutic latency. He suggests that the acute antipsycholeptic effect of neuroleptics is relatively a nonspecific deactivation or sedation and that over time, as supersensitivity develops, this sedation is alleviated. It is customary to think of the supersensitivity developing only to dopamine because the neuroleptics block dopamine receptors; in compensation, more dopamine receptors are formed.

Supersensitivity, however, may develop not only to dopamine, but also to other neurotransmitters. At the same time, still other systems may become subsensitive, especially the receptors for the excitatory amino acid, glutamate. Freed speculates that subsensitivity to glutamate is responsible for the antipsychotic effect of neuroleptic medications. This subsensitivity would take several weeks—approximately the same time it takes for neuroleptic medications to have their optimum clinical effect—to develop.

Shore's work moves us out of the laboratory and into the clinic. An important part of clinical practice with psychotic patients is the ability to predict violence. He discusses the unusual group of paranoid schizophrenic individuals that attempts to see the President of the United States or other prominent political figures. Because of their hallucinations, delusions, and bizarre behaviors, these individuals are considered to be a potential threat. Demographic characteristics such as prior violent crime arrest and male gender proved to be much better predictors of future violence than clinical symptom, history, or behavior items. Hospital incidents requiring seclusion and a history of weapons possession were both associated with later violence in White House Cases (WHCs) with prior violent crime arrests, while certain clinical symptoms (e.g., persecutory delusions and command hallucinations) may be linked to future violence in WHCs without prior violent crime arrests.

Kirch et al. look at the relationship between serum concentrations of the neuroleptic haloperidol and clinical response. For clinicians and basic scientists alike, it would be very helpful if blood concentration could be used in adjusting dosage. Blood concentrations of anticonvulsants have been very important in treating seizure disorders; blood levels of lithium are crucial in treating bipolar illness. Haloperidol, the most frequently prescribed neuroleptic, has been proposed by some investigators to have a “therapeutic window”—a curvilinear relationship between the clinical response and the medication concentration wherein at both low and high concentrations there is an association with poor clinical response. Using a fixed dose of haloperidol, Kirch and his colleagues found that patients appear to plateau in their response. There may be a concentration above which blood levels have to reach for a response to be achieved, but at higher levels the response may not be significantly better or worse. Perhaps there is no therapeutic window, only a threshold.

A serious adverse effect of neuroleptic treatment is the movement disorder, tardive dyskinesia. Lohr et al. have given vitamin E (α-tocopherol) to patients with tardive dyskinesia in a placebo-controlled, double-blind, crossover study. During the treatment period, abnormal movements decreased by 43
percent. This improvement did not occur during placebo. The effect was much greater in patients with tardive dyskinesia than in those with tardive dystonia. This is intriguing work that certainly merits replication.

The Future

In addition to the contributors to this issue of the Bulletin, many other noteworthy researchers of schizophrenia have been or are still with the Intramural Research Program. The 19 articles presented here, curtailed in length and breadth by the need to fit them into a single issue, cannot cover the Program's entire range of creative efforts. The work described does, however, reflect much of our rich heritage and, we hope, foretells much important work yet to be performed. It is a fine "record of what [has] had to be done . . . by all who . . . strive their utmost to be healers" (Camus 1972).

References


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