Research News

Biological Issues in Schizophrenia

Amid controversial theories about the biology of schizophrenia, genetic factors, altered brain dopamine systems, and structural abnormalities in the brain may play key roles

THE history of research on schizophrenia is littered with ideas that gained rapid popularity and then died from a lack of sustaining data. Some of the current theories about the biology of this mental disorder—its origin and the disease process itself—will probably meet a similar fate. But a movement is under way, stimulated by modest increases in funding for research on schizophrenia (see box), to identify and pursue the most promising leads for unraveling the biology of this mental illness.

Schizophrenia affects an estimated 0.5% to 1.2% of the United States population and inflicts an enormous financial and personal cost. At nearly every biological level imaginable, the often incapacitating mental disorder defies specific classification. It is characterized by delusions, associations of unrelated ideas, and hallucinations, and by social withdrawal and a lack of emotional responsiveness, motivation, and sense of self. The causes of schizophrenia are unknown, and no functional or structural changes in the brain can unequivocally be associated with the disease.

Speaking at a recent meeting in West Berlin, "Biological Perspectives in Schizophrenia,"* Kenneth Kendler of Virginia Commonwealth University in Richmond summarized his views on the most important research findings on schizophrenia. "If you put everything that is known about schizophrenia into a pot and boiled it down you would come up with three things—it seems to run in families, neuroleptics [drugs that interact in some way with the brain's dopamine system] make it better, and there may be something structurally abnormal in the brains of schizophrenics."

Basic to all of the research strategies is the hope that new techniques for studying the brain directly will reveal more about the biology of schizophrenia. Physicians and scientists can now use imaging techniques, measurements of blood flow and metabolism, and receptor mapping to monitor brain structure and function in living patients. And although neuroscientists have yet to find clear biological markers for schizophrenia, some anticipate that they may be able to use molecular biological techniques to probe possible genetic defects associated with the condition.

Arvid Carlsson *proposes that a disintegration of the brain's dopamine system may lead to some of the symptoms associated with schizophrenia.*

Researchers continue to debate whether schizophrenia represents a discrete mental disorder, or is just one component of a spectrum of mental illnesses. Ming Tsuang of Harvard Medical School thinks that the current data favor the former, traditional concept of two discrete, major psychoses. One is schizophrenia, which starts during adolescence and usually becomes worse, and the other includes affective (mood) disorders, which occur in episodes and are less likely to incapacitate the patient. But he says, "to really nail this down, we need to have molecular genetics studies to show whether the two diseases are different at the molecular level."

Timothy Crow of Northwick Park Hospital in Harrow, England, has a different perspective and sees affective illnesses and schizophrenia as being at opposite ends of a continuum of psychotic disorders, rather than being separate disease entities. At one end of the spectrum is depression, followed by manic depression, mixed schizophrenia and affective disorder, and schizophrenia without accompanying affective disorder. Crow emphasizes that "the people in the middle of the spectrum are much more common" than those at either extreme.

Steven Matthysse of McLean Hospital in Belmont, Massachusetts, emphasizes the uniqueness of the thought disorder in schizophrenia. "Although both manic-depressive patients and schizophrenics have disturbed thinking, the way schizophrenics think is special," he says. "It is so distinct that it may be used to define the disorder."

The lingering debate about what constitutes schizophrenia complicates the search for its cause or causes. However, most of the existing information indicates that something about schizophrenia is inherited, according to Seymour Kety of the National Institute of Mental Health (NIMH).

Much of the evidence to which Kety refers comes from studies of identical twins—more than 50% of the time, if one twin develops schizophrenia, the other does, too. Further support for the genetic theory comes from adoption studies. Children of schizophrenics who are adopted by nonschizophrenic parents have a higher incidence of schizophrenia than a control population.

But some researchers think that the genetic hypothesis of schizophrenia may be overemphasized. Daniel Weinberger of NIMH cites published data. "What you can show is that the first-degree relatives of schizophrenics have a very slightly higher [3% to 7%] likelihood of developing the disease, but more than 90% of the relatives of schizophrenics do not have schizophrenia according to current diagnostic criteria."

The genetics of schizophrenia is not likely to be clear-cut, according to defenders of the theory. "It is not fair to say that schizophrenia is a genetic disease; it is not a classic Mendelian trait inherited like the gene for Huntington's chorea," says Kendler. "But the evidence is strong that schizophrenia, like coronary heart disease and early-onset hearing loss, tends to run in families."

Currently, the two hypotheses about the inheritance of schizophrenia receiving the most serious consideration are a model based on a single major gene locus, supported by Philip Holzman of Harvard University and Matthysse, and a model that proposes multiple genetic causes, which Tsuang advocates. But pinpointing the modes of inheritance or the number of genes involved depends on data that do not yet exist and which all agree are essential to obtain.

*The Dahlem conference on "Biological Perspectives in Schizophrenia" was held in West Berlin from 26 to 31 October 1986. Proceedings of the meeting may be obtained from Dahlem Konferenzen, Wallostrasse 19, D-1000 Berlin 33, Federal Republic of Germany.

Nevertheless, Holzman and Matthysse propose that a "latent trait" exists for both schizophrenia and a possible biological marker for the disease—poor eye tracking. The researchers find that about 65% of schizophrenics (as opposed to 8% of the normal population), and about 45% of their first-degree relatives visually follow a moving object in interrupted movements rather than in a smooth, fluid motion.

Holzman, Matthysse, and their colleagues have just completed a study of eye tracking in two generations of offspring of schizophrenic twins. "In the branch of the family in which the gene is being transmitted, we predicted that about 30% of the people would show poor eye tracking, and that is what we found," says Holzman. This does not mean that everyone with poor tracking carries the gene for schizophrenia. "We think that poor eye tracking is a manifestation of the underlying disease process in those families," says Matthysse. "What we have really shown is that a simple genetic model—with a single dominant gene—fits the data surprisingly well."

Questions remain about poor eye tracking as a biological marker for schizophrenia, however. Although Nikki Erlenmeyer Kimling of the New York State Psychiatric Institute supports poor eye tracking as a potential marker, she is "worried that it sometimes doesn't occur in the patient when it does occur in a relative." For a trait to qualify as a good marker, she says, it must exist before someone ever shows psychotic symptoms of schizophrenia, be found at times between episodes, and indicate who is at risk for the condition. These criteria are not fulfilled by poor eye tracking.

Lynn DeLisi of NIMH points out that poor eye tracking is not specific for schizophrenia; people under the influence of certain drugs such as alcohol or barbiturates and patients with Parkinson's disease, multiple sclerosis, and certain brain lesions also track poorly.

The failure of the inheritance data to explain a cause for schizophrenia leads other researchers to seek possible nongenetic causes. For instance, Crow suggests that a retrovirus could infect healthy individuals, which might help to explain the unusually high prevalence of schizophrenia. If such a virus incorporates into the human genome, it could be passed from one generation to the next and account for the apparent heritability of schizophrenia.

The list of putative causes for schizophrenia is long and inconclusive. In the absence of hard evidence for any "viral hypotheses" of schizophrenia, some advocates point to data that slightly more (54% of the total) schizophrenics are born in winter or spring

A Top Priority at NIMH

Schizophrenia—or, more accurately, the schizophrenias—is the "cancer" of the mental illnesses. But, unlike cancer, it is still the object of public stigma and ignorance, and no "war" has been mounted against it. Whereas the government spends $300 on research for every cancer sufferer, the comparable figure for schizophrenia is about $17. Since the disease, which afflicts 1% of the population, is not fatal, lifetime costs of care are staggering. The Institute of Medicine has estimated that treatment and lost productivity cost the country $48 billion a year.

The National Institute of Mental Health (NIMH) is now trying to make schizophrenia research a top priority. The reorganization of the institute 2 years ago was effected mainly with an eye to emphasizing research on the major mental illnesses, and extramural research and training programs are now combined in the Schizophrenia Research Branch, headed by Samuel Keith, within the Division of Clinical Research. The staff has been more than doubled, to 13. A new clinical research lab headed by Daniel Weinberger is planned for the intramural research division. In addition to the Clinical Research Center at the University of California (Los Angeles), two new centers devoted to schizophrenia research have been designated, at the University of Maryland and at Long Island Hillside Hospital.

Congress tacked on $5 million to the fiscal 1987 research budget to be targeted to schizophrenia, making for a total extramural commitment of $20.4 million in addition to $10.1 million for intramural research. The fiscal 1988 presidential budget would keep the funding steady despite a 5% cut in the rest of the NIMH research budget. According to Keith, though, the field could readily absorb a tenfold increase in funds because of the rapid advances in brain imaging and biochemistry that have occurred within the past 5 or 6 years.

Until now, says Keith, schizophrenia research has been "something of a cottage industry." Now, he says, it is time to "address it in a major science way." Scientific leads have been a long time coming, in part because of the grip of psychoanalytic theories of mental illnesses which did not loosen until the 1970s when the revolution in biological psychiatry finally unseated psychosocial factors as the primary etiological suspects for schizophrenia. The political climate has also changed, with the rapid growth of organizations of the families of the mentally ill. The increase in the homeless population, one-third to one-half of whom are believed to be schizophrenic, has also made the problem painfully visible.

Developing a cadre of trained and committed schizophrenia researchers is still a problem. As Keith notes, schizophrenics are a specially difficult population to work with. For many years, the disease was regarded as hopeless and researchers were more attracted to the fast-breaking developments in the chemistry and treatment of emotional disorders.

NIMH convened a meeting in 1985 on incentives and disincentives for schizophrenia research careers where researchers agreed that "an overwhelming problem is the lack of a comprehensive theory," the development of which has been stymied by the "clinical and biological heterogeneity" of the disease. The dopamine theory is useful but by no means covers all the bases, as evidenced by the fact that 20% of sufferers do not respond to antipsychotic drugs. Researchers said the "nonspecificity" of many findings make other areas more intellectually satisfying. Alzheimer's disease, in particular, looks more promising to those wanting to make a career in brain research. (In 1980 the budgets for schizophrenia and Alzheimer's were comparable; now the Alzheimer's budget is double that for schizophrenia.)

Getting good research subjects is difficult. Schizophrenia, being chronic and financially debilitating, is not treated as often as is, for example, depression, in academic settings. This has made for a separation of clinical care and academic research. Keith says subjects are needed both at the "front and tail ends." That is, researchers need to study the chemistries of schizophrenics while they are still "drug virgins," which means that a major effort has to be made to refer patients to research centers before treatment. At the tail end are the chronic, treatment-resistant patients who end up in state hospitals and who rarely become research subjects.

Modest increases are being made in support for manpower development in schizophrenia research. But Keith says "people are still skeptical, they fear the spigot will be turned off again—they need to expect a stable base. It will take time." ■

CONSTANCE HOLDEN

Seymour Kety (left) and Ming Tsuang

discuss possible modes of inheritance for schizophrenia.

months when viral infections are frequent than are born during summer or fall months. But the fact remains that no virus or consistent evidence of viral infection can be associated with schizophrenia. Disorders of the immune system, possibly triggered under conditions of stress, have also been suggested as a cause for schizophrenia, as have obstetric complications, particularly anoxia at birth.

Göran Sedvall of the Karolinska Institute in Stockholm, Sweden, summarizes the viewpoint held by some researchers that "a complex interplay of genetic and environmental factors" probably determines the likelihood that someone will develop schizophrenia.

A second major area of research in schizophrenia concerns the disease process itself, specifically the likelihood that one or more neurotransmitter systems may be abnormal. The brain's dopamine system is currently receiving the most attention. Although abnormalities in dopamine neurotransmission may not cause schizophrenia, many researchers now think that they are probably important in the disease process.

"We have 40 or 50 drugs that decrease the symptoms of schizophrenia, and they all work through the dopamine system," says Fritz Henn of the State University of New York at Stony Brook. But he also emphasizes that these neuroleptic drugs work against the psychotic symptoms of schizophrenia and may not necessarily act to correct a brain defect fundamental to its cause.

Nevertheless, more and more evidence points to the possibility that, in the brain of a patient with schizophrenia, the influence of neurotransmission mediated by dopamine may be too great. This does not necessarily mean that there is too much dopamine, which researchers estimate is produced by only about 1% of all the neurons in the brain. Instead, new evidence from the laboratories of Sedvall and of Dean Wong and Henry Wagner, at Johns Hopkins University School of Medicine, indicates that there may be an increased number of receptors for dopamine, rather than higher levels of the neurotransmitter itself.

The new data reported by Wong and his colleagues appear to resolve a long-standing dispute about whether increases in dopamine receptors in the brains of schizophrenic patients are characteristic of the disease or are secondary to drug treatment. Positron emission tomography scans of the brains of living patients show that, in both drug-treated and untreated schizophrenics, the caudate nucleus has significantly higher than normal levels of binding to D_2 dopamine receptors. The increase in receptors therefore seems intrinsic to the disease and not a result of drug treatment.

Steven Bunney of Yale University School of Medicine questions whether an increased number of dopamine receptors in the caudate-putamen nucleus has direct significance in schizophrenia. This part of the brain is primarily involved in movement disorders, such as Parkinson's disease. Bunney and his colleagues focus instead on changes in dopamine pathways that, if perturbed, might result more directly in thought disorder. These include the dopamine neural projections from the midbrain to the prefrontal cortex and the limbic system.

Antipsychotic drugs, which are used to treat schizophrenia, block dopamine receptors on both dopamine-releasing cells in the rat brain and on other neurons that release different transmitters. Although the drugs have both acute and long-term effects, Bunney doubts that the short-term effects are responsible for their therapeutic activity in schizophrenia. "People worked on the acute effects of these drugs for years," Bunney says. "But antipsychotic drugs work in a time-dependent way, not acutely."

Usually patients must receive antipsychotic drugs for at least a week before symptoms such as thought disorder begin to improve. After several days to weeks of treatment, neurological symptoms, such as parkinsonian-like effects, may appear. And after months to years of continuous treatment, 10% to 40% of patients may develop tardive dyskinesia, with abnormal involuntary chewing and facial movements. This condition apparently stems from a drug-induced increase in sensitivity to dopamine.

Researchers do not know precisely how antipsychotic drugs exert their time-dependent effects in humans, but data from animal studies suggest that their long-term blockade of dopamine receptors ultimately leads to a decreased release of dopamine. With a drop in dopamine release, less of the neurotransmitter is available to compete with antipsychotic drugs for receptor binding sites. This may lead to both therapeutic benefits and adverse side effects. If the level of overall dopamine activity in the brain—as determined by a combination of dopamine release and receptor binding—drops too low, patients may experience parkinsonian-like side effects. But with the right balance between receptor blockade and dopamine release, patients may also be relieved of their psychotic symptoms.

As the research on what is abnormal about the dopamine system in schizophrenia proceeds, the results begin to come together. Arvid Carlsson, of the University of Göteborg in Sweden, identified the likelihood of a dopamine abnormality in schizophrenia more than 20 years ago. He now hypothesizes that a disintegration of the brain's dopamine system may lead to the high mental arousal state associated with schizophrenia.

Citing data from animal studies, Carlsson explains how too much influence of the dopamine system might result in abnormal behavior. "If we give increasing doses of drugs that mimic dopamine, they induce an increase in the animal's locomotor activity," he says. "But at a certain level of dopamine, we see an abnormal stereotyped behavior. The animal stops moving around and begins to show all kinds of purposeless movements such as licking and head bobbing. It is as if the whole repertoire of activity that was normally integrated is now disintegrated." He proposes that a similar disregulation of the dopamine system in man—whether due to an abnormally high level of dopamine drive or to lack of regulation by the cerebral cortex—may be important in schizophrenia.

A third area of research in schizophrenia concerns the possibility of structural abnormalities in the brain, an idea that has been given new life with the advent of brain imaging techniques. For example, some researchers use computerized tomography (CT) scans and magnetic resonance imaging of a living patient's brain to observe gross changes in brain structures, including enlarged ventricles or atrophy in specific brain regions. Other techniques rely on measurements from postmortem tissue. Researchers report a reduced volume of limbic structures, the hippocampus and amygdala in particular, or an abnormal arrangement of neurons in these brain regions.

DeLisi acknowledges that recent evidence points to structural lesions in the brains of schizophrenics, especially in the limbic system and parts of the neocortex. But she notes at least three areas of controversy related to the findings. First, many of the studies have methodological problems, and not everyone agrees on how the results should be interpreted. Weinberger concedes that, whereas psychiatrists who study brain abnormalities in schizophrenia report enlarged ventricles, neuroradiologists regard the same CT scans as normal. But the real controversy, he says, is whether a subtle change in ventricular size has clinical meaning.

Second, DeLisi points out that "these changes, at least in the ventricles and those in the temporal lobe of the cortex, are not specific to schizophrenia." And third, she sees a discrepancy between the static nature of a structural lesion and the very nonstatic course of the disease. The idea is that, if the brain abnormality is there all the time, then why do patients with schizophrenia experience episodes of disease?

Researchers also observe abnormalities in the prefrontal cortex of schizophrenics. Some patients, particularly those who are older and mentally deteriorated, have reduced blood flow in the frontal and prefrontal cortex as compared with other brain regions. This hypofrontality, as it is termed, may result from either a primary defect in the cortex or exist because nerve pathways that project to that area are abnormal, according to David Ingvar of University Hospital in Lund, Sweden.

Recently, Weinberger, Karen Berman, and Ronald Zec, all of NIMH, reported that young schizophrenic patients also display hypofrontality. "But only when there is a need for increased neuronal function in the prefrontal cortex is the deficit seen," says Weinberger. The NIMH group finds that the Wisconsin card-sort test—in which patients try to sort cards in a new way when the tester indicates that the present sorting method is incorrect—specifically requires the function of the dorsolateral region of the prefrontal cortex. A nonschizophrenic person performs the test easily and shows increased blood flow to the prefrontal cortex during the task, but schizophrenic patients fail to find new ways to sort cards and show no increased blood flow.

But again, experimental results are not consistent. Not all schizophrenics exhibit reduced blood flow to the prefrontal cortex, people with other neurological conditions show similar deficits, and not all neuroscientists accept the card-sort test as a specific physiological demand of prefrontal cortical function. Still, many researchers think that abnormalities of the prefrontal cortex, including metabolic function, dopamine activity, and possible structural changes, warrant further investigation.

A related area of schizophrenia research focuses on asymmetries in the brain. Recent work by Gavin Reynolds reveals that the amygdala on the left side of the brain of some schizophrenics has an increased dopamine content, whereas the right amygdala does not. But whether this and other indications of asymmetry are part of the disease process or simply reflections of the brain's natural asymmetry have yet to be determined.

Because the symptoms of schizophrenia that first require treatment often appear in early adulthood, some researchers are beginning to ask whether milder pre-schizophrenia symptoms occur even earlier and whether certain developmental processes in the brain that take place around puberty may be related to schizophrenia. More males are diagnosed with schizophrenia before age 25, and early onset often means a poorer outcome. Whether a second category of psychotic patients, whose symptoms appear at 60 years or older, differs at least in terms of the cause of psychosis is also being investigated.

For every point of view about the biology of schizophrenia there is a counterpoint. Theories about the origin and disease process of schizophrenia are often built on a multitude of empirical observations and a paucity of hard facts. Differing and sometimes contrasting interpretations are applied to the data that do exist. Sometimes experiments are poorly designed. But the looming issue is the overwhelming complexity of schizophrenia. New techniques and attempts to integrate existing data into coherent theories may soon produce some understanding of the mental disorder that afflicts 1.5 to 2 million Americans. ■

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A Geophysics Potpourri In San Francisco

When the American Geophysical Union and the American Society of Limnology and Oceanography held a joint meeting last December, the result was 5000 registrants and 20 to 30 simultaneous sessions for 5 days. The meeting encompassed everything from the feeding habits of zooplankton to galactic cosmic rays, so it cannot be summarized. Here are a few samples of the varied fare.

Getting a Full View of The Earth's Innards

For more than 10 years geophysicists have had two complementary means of imaging the earth's crust and the upper mantle below it—refraction seismology and reflection seismology. Within the past few years researchers have gone from largely independent, uncoordinated, and often small experiments involving one or the other technique to large, multi-institutional experiments combining both approaches at the same site. To judge from talks and posters at the meeting, combined experiments are becoming de rigueur. The early results are promising.

George McMechan of the University of Texas at Dallas and Randy Keller of the University of Texas at El Paso reported early results from an experiment in southern Oklahoma, the largest such seismic experiment ever conducted by academic institutions. Eight hundred seismometers with six sensors each were deployed in three steps along a 100-kilometer line across the sediment-filled Anadarko Basin and the Wichita Uplift. Every 2 milliseconds these seismometers recorded the waves generated by 25 separate borehole blasts of 130 to 1600 kilograms of TNT. That left the experimenters with 13 billion bytes of data.

This vast amount of data required 2 years of effort to develop and apply useful processing techniques, but now the two types of seismic wave data are in good shape, says Keller. The refracted waves, which traveled