SCHIZOPHRENIA:

From Adolescent Insanity to Dopamine Disease

BY WRAY HERBERT

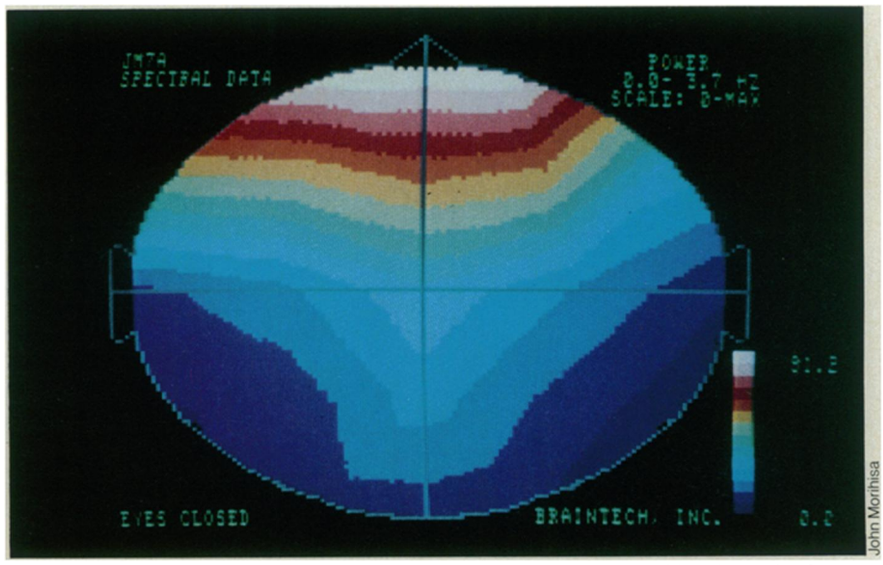
"Is there no way to cure this? No new device to beat this from his brain?"
—William Shakespeare

Psychiatrist Adolf Meyer, speaking before the American Medico-Psychological Association in the early 1920s, urged upon his colleagues what was then a fresh term and concept — schizophrenia. In doing so, Meyer was suggesting that psychiatry discard the notion of "dementia praecox," which since the mid-1800s had become a kind of diagnostic trash bin for those "hopeless" forms of insanity that could not be fathomed — much less cured. Meyer was echoing the sentiment of the Swiss psychiatrist Eugen Bleuler, who coined the term schizophrenia from Greek roots a few years earlier, that such disorders came in many forms, some less hopeless than others.

Though schizophrenia did supplant dementia praecox in the psychiatric vocabulary, the change in labels did not end the disagreement about just what schizophrenia is. It remains as baffling a disease today as it was in the 1920s, characterized by disorganization of thought and an unsettling emotional flatness. It is often accompanied in its acute phases by florid psychotic symptoms—delusions, hallucinations, catatonia. Once called "adolescent insanity" because of its typical time of onset, schizophrenia in its harshest forms leads to complete social withdrawal. Bleuler's term was a descriptive one: schizophrenia is best translated as disorganized personality.

Schizophrenia has been called the greatest psychiatric challenge. Ever since the concept came into professional use, researchers have been involved in an intense effort to sort out the schizophrenias and to identify their causes and cures. It has been largely an unsuccessful effort, most researchers freely concede, but it has not been a fruitless 60 years. Although by some estimates the disorder continues to afflict 1 of 100 people, disparate lines of research over time have turned up bits of evidence about what goes on in the schizophrenic mind — clues about cognition, chemistry, and physiology—that some researchers predict will soon begin falling into place.

Like many fields, schizophrenia research has been ruled by fashions. But while psychoanalytic and existential theories have had their hours, the dominant interest of researchers has from the beginning been the schizophrenic brain. And the central research dilemma has been how to get at such an inaccessible organ, to observe it, and measure it and pinpoint its dysfunction.



John Morihisa

Computer analysis of EEG *data produces a Brain Electrical Activity Map* (BEAM) *of a patient with schizophrenia.*

Psychiatrist Emil Kraepelin hypothesized in 1896 that dementia praecox was a metabolic disorder similar to paresis. Toxic substances, he believed, were coursing through the bloodstream and damaging the cortex. This general theory held sway into the 1930s, early psychiatric journals reveal, but despite the appeal of the theory researchers had little success in identifying the guilty toxin. Kraepelin himself suspected the ovaries and testes because of the high incidence of schizophrenia following puberty, but his "sex intoxication theory" was never borne out.

In 1935, psychiatrist Nolan Lewis reviewed some 1,800 research reports on schizophrenia published since 1920 and concluded that "research is in a state of chaos." Indeed, early journals carry reports on almost anything that could conceivably be measured or weighed: carbohydrate metabolism, blood circulation, heat regulation, heart size, muscle fatigue, blood vessel rigidity, iodine in the brain, protein in the spinal fluid, potassium in the blood. Body types were studied (schizophrenia was associated with frail, "asthenic" build); liver disorder was suspected, as was the tuberculosis bacterium. Endocrinology was a growing field, a fact reflected in Lewis' observation that "practically every gland has, at one time or another, been incriminated as the chief etiological factor."

Every passing fancy about the causes of schizophrenia was accompanied by a treatment for the disorder, according to Samuel J. Keith, director of the National Institute of Mental Health Schizophrenia Studies Center. "Back in the twenties tooth removal was a common treatment for schizophrenia, because it was thought that focal infections in the mouth were producing some sort of toxin. The same thing happened with colonic irrigation, dropping people down wells, injecting them with coloidal gold or deactivated horse serum. And it continues into the modern day," Keith notes. "We have hemodialysis now, which is intended to sweep out the psychotogens. History refinds itself."

The reason such treatments recommend themselves is that almost every line of research, in the twenties as today, reveals that at least some schizophrenics differ from normals. In the twenties and thirties schizophrenics were found, among other things, to have smaller hearts, to suffer disproportionately from tuberculosis and to have lower rates of metabolism. But almost all of these differences were later explained as artifacts of institutionalization and poor care. According to psychiatrist Leopold Bellak of the Albert Einstein College of Medicine, who has reviewed schizophrenia research over 40 years, the early work, without exception, produced nothing of value.

Researchers generally agree with Bellak, although some argue that early investigators occasionally had good ideas but lacked the technology to pursue them. As early as 1928, psychiatrists hypothesized a

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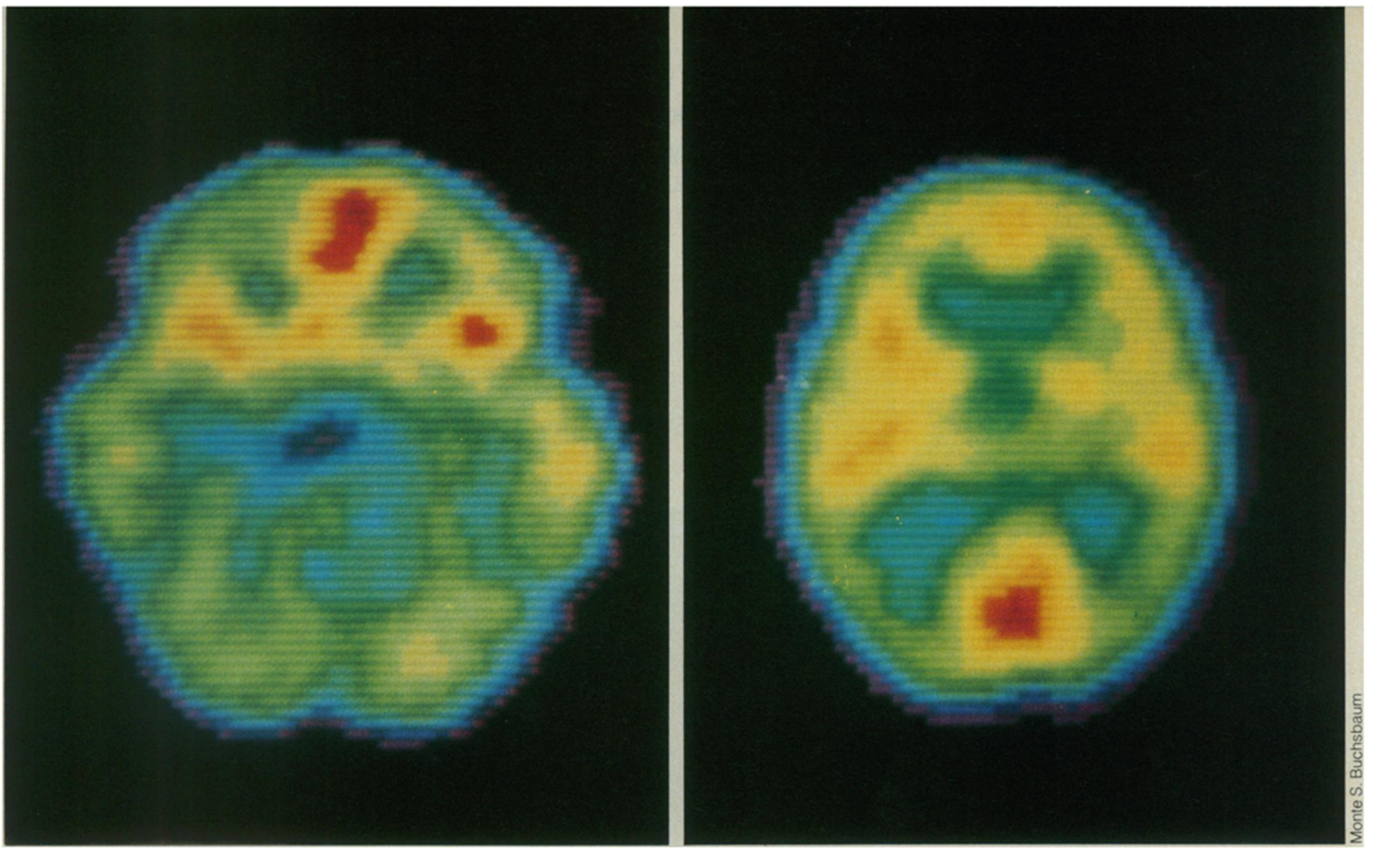

constitutional predisposition for schizophrenia, suggesting that special brain systems, not yet identified anatomically or physiologically, might be vulnerable to psychic or physical trauma. The field was dominated by attempts to approach the still mysterious brain. In his 1935 review, Lewis mentioned the intriguing project of Hans Berger, who had developed an electroencephalograph (EEG) capable of measuring electrical activity, or Berger waves, coming from the brain. The EEG was still primitive — it required piercing the scalp. And its findings — that schizophrenics had unusual alpha and beta wave patterns — were of little use. Other primitive brain research was also suggestive: early pneumoencephalograms revealed slightly-enlarged ventricles in schizophrenic brains; others observed that schizophrenics had difficulty with smooth eye movement; still others noted differences in cerebral blood flow, anticipating what have become productive lines of research. According to Menninger Foundation psychologist Herbert E. Spohn, "We're finding in the literature that people did the same things with cruder methods but greater ingenuity in the twenties and thirties. But they didn't follow up; the technology wasn't there."

The work of most lasting value from before 1940, according to Harvard psychiatrist Seymour Kety, was the research done by psychologist David Shakow as part of a massive and protracted project at Worcester State Hospital in Massachusetts. As the first psychologist to use the methods of the psychological laboratory for the systematic study of schizophrenic behavior, Shakow turned out findings on motivation, thought processes, reflexes, cooperation and competition, and — most notably — reaction time. "Before Shakow," says University of Minnesota psychologist Norman Garmezy, "the schizophrenic was viewed as an enormously deficit-ridden organism. Shakow asked, 'Does a specific deficit exist, and if so at what level?'" What he found was that at the most fundamental reflex level schizophrenics appeared to suffer no deficit, but at the level of will and motivation they did. Following up on that, Shakow demonstrated that the motor abilities of schizophrenics could improve to the level of normals with continuous performance of certain tasks. These were revolutionary findings concerning a patient population previously viewed as chronically disabled, researchers say.

Shakow's work on reaction time led to his influential theory of "segmental set," setting the stage for much of the later work on attentional deficit in schizophrenia. He asked why schizophrenics could not attend to tasks and found, through a series of experiments, that many irrelevant or fleeting thoughts intrude upon the consciousness of schizophrenics and compete with the "experimental set" which keeps normals focused on a task. This "disattention" was revealed as a complex cognitive phenomenon, spawning a research endeavor that has since enveloped information processing theory and provided increasingly sophisticated insights into schizophrenic cognition.

The most significant change in schizophrenia research since the 1920s, researchers say, has been the dwindling interest in searching for the "silver bullet" that would finally cure the disorder. Because of the failure to identify the specific biological mechanism underlying schizophrenia, biological work came to somewhat of a standstill during the forties and fifties, while people like Shakow concentrated on understanding psychopathological behavior. But in the late 1950s, the dream of a single biological bullet was renewed.

Perhaps the only real breakthrough in schizophrenia research occurred purely by chance. Certain drugs used during the Indo-Chinese War with France to induce hypothermia for battlefield surgery were found to make grievously injured soldiers quite serene, and in a very short time the psychotropic properties of the so-called neuroleptic drugs became well known.

The drugs revolutionized the treatment of schizophrenia by markedly reducing or removing psychotic symptoms, and they enticed a new generation of psychiatric researchers into the promising field of biochemical brain research. In 1963, Arvid Carlsson of Sweden determined that the neuroleptics produced their effects by affecting the level of dopamine, a neurochemical transmitter in the brain. Then in the seventies, Johns Hopkins psychiatrist Solomon Snyder, then at NIH, discovered that dopamine works in the brain by binding to certain protein receptors. With those back-to-back findings, the dopamine hypothesis for schizophrenia was launched. Neuroleptics work by blocking dopamine receptors, preventing chemical transmission. Certain drugs such as amphetamines, which release dopamine, exacerbate psychosis in schizophrenics and, in large doses, can even create psychosis in normal subjects. Thus the dopamine hypothesis relates schizophrenia to an excess of dopamine activity in certain brain pathways.

Nearly as rapidly as interest in dopamine ascended, however, researchers became disenchanted and discouraged. First of all, researchers explain, dopamine is very difficult to study. Almost all dopamine activity takes place in the lower

PET *scans of schizophrenic patients (right) and a normal volunteer show contrasting patterns of glucose metabolism. Patient was hallucinating, which may explain activity in visual and auditory regions of brain.*

German psychiatrist Emil Kraepelin used this photograph of schizophrenic patients to illustrate his 1919 volume Dementia Praecox and Paraphrenia.

brain — including the limbic system, which is involved in human emotions — but those structures are inaccessible for study; as a result, scientists have had to estimate dopamine levels by measuring markers in the blood, urine and spinal fluid. The most promising of these biological markers has been an enzyme called monoamine oxidase (MAO), found in blood platelets, which is known to break down dopamine; but lately low MAO has been found in various disorders, and many suspect that it is an artifact of drug treatment.

Furthermore, many psychiatrists now say a simple dopamine theory just doesn't work. According to University of Chicago psychiatrist Herbert Meltzer, who has been studying neuromuscular abnormalities in schizophrenics, certain reflex deficiencies characteristic of schizophrenia are consistent with decreased — not increased — dopamine activity. Neuroleptics are not effective for some patients, he notes, and indeed the converse has been demonstrated: schizophrenics have been successfully treated with amphetamines. "It is clearly not a simple matter of too much dopamine," Meltzer concludes. "Many aspects of the syndrome can be attributed to too little dopamine." The dopamine system has been found to be complexly interrelated with other neurotransmitter systems and with neuroendocrine functions. And as the complexity of the system has become more and more apparent, interest in biochemical notions of schizophrenia has waned, according to psychologist Terry Patterson of the Menninger Foundation. "A few years ago everybody was running around battling for his sacred neurotransmitter. There was the cholinergic theory, the dopamine theory, the serotonin theory — but life is just not that simple. No neurotransmitter ever acts in isolation."

Though a few researchers are ready to scrap the various chemical theories, most suggest a more modest estimate of their value. "One mistake researchers have made," Bellak notes, "is that they expect a hypothesis to hold true for all schizophrenics. If for 50 percent the dopamine hypothesis does not hold true, it may be that those people are not dopaminergic schizophrenics; but it may well be true that the other 50 percent are." While psychiatrists since Bleuler have paid lip service to the notion that schizophrenia is a syndrome —a group of disorders with similar symptoms—they have rarely applied that belief in research, Bellak explains. As a result, if a suspected biological trait has not been found in all schizophrenics, it has been discarded as unuseful rather than interpreted as an indicator of a schizophrenic subtype. Today, however, a willingness to look for biological subtypes of schizophrenia is becoming more and more common.

Researchers are also taking a fresh look at certain early findings which may have been prematurely put aside: enlarged ventricles and cortical atrophy, first identified in the 1920s, are now suspected as markers of a specific kind of schizophrenia; eye-tracking disabilities observed as early as 1908, now known to be mediated by neurochemicals, are consistently seen in some schizophrenics and their relatives; skin conductance measures have been used to separate schizophrenics with poor and excellent abilities to concentrate on cognitive tasks. "Schizophrenia may be like mental retardation, with many identifiable causes," says Brown University psychologist Richard J. Haier. "It may be that 30 percent of schizophrenics have a dopamine disease, and that 30 percent have something else wrong — perhaps a nutritional disorder. Maybe 10 percent have brain damage."

Connecting advancements in biological psychiatry with psychological insights into schizophrenic behavior is the task at hand, many researchers now say. With the development of sophisticated small computers during the fifties, EEG research — mentioned in passing by Lewis in 1935 — had developed powerful capacity for measuring brain waves associated with very specific external stimuli — visual, auditory, cognitive and emotional stimuli. Motivation and will, as Shakow demonstrated, play a crucial part in pathological cognition, and so-called "evoked potential" research make it possible to study basic cognitive processing through precise measures of nervous system arousal; attention can in effect be divorced from volition and analyzed. According to Spohn, brain wave responses can now be broken down into early, middle and late stages, each lasting only milliseconds, to determine whether a deficit is related to preattentive registration of information, active processing, or memory.

As EEG research strategies evolved, other technological advances were taking place. More elegant software gave computerized tomography (CT) scanners the capability to locate brain structures previously indetectable; positron emission tomography (PET) and xenon inhalation tomography gave researchers the ability to observe glucose metabolism and cerebral blood flow related to specific experiences — auditory hallucinations, for example. "These are all windows on the schizophrenic brain, but each offers a slightly different angle," says psychiatrist John Morihisa of the NIMH adult psychiatry branch. "If we can synthesize all these views, we may be able to piece together patterns of the disease." Morihisa — together with Harvard neurologist Frank Duffy — is planning to use computerized brain mapping, in combination with measures of cerebral blood flow, eye tracking, and neurochemical activity, to explore possible links among suspected indicators of schizophrenic subtypes. Similarly, Monte S. Buchsbaum of NIMH has been using a PET scanner to observe the schizophrenic brain engaged in specific cognitive tasks, with and without neuroleptic drugs. The trick in such synthetic research is to make the connection between electrophysiological indicators of cognitive disorders and the lower brain, where the important neurochemical activity is presumably taking place.

One approach, now being taken by psychologist Rue Cromwell and geneticist Lowell Weitkamp of the University of Rochester, is to combine biological, neurophysiological and attention measures in studies not only of schizophrenic patients but of their extended families as well, to determine what abnormalities are transmitted genetically. Another approach is to actually monitor the activity in pathways connecting lower brain and cortex. Patterson has taken computerized brain mapping a step further in his examination of the connection between a specific cognitive deficit and deep brain abnormality. Schizophrenics are known to have problems with early visual learning and Patterson suspects that the problem involves the lower brain, which sorts through incoming noise to relay coherent messages to the cortex. If the relay system were malfunctioning, the cortex would be overstimulated and thus distracted from the visual image that begins the cognitive process. Patterson has built a 40-channel EEG with the capacity to measure electrical potentials in the brain stem as it relays information to the cortex. If there is an abnormality in the relay of information to the cortex, the dopamine system could be conceptually linked to a specific behavioral deficit. "Everybody wants an explanation of neurochemical nature which in turn controls the rate of bombardment along pathways of mental flow from one part of the brain to another," Patterson says. "That will be the true functional interface, because it will be that which, if we tweak it, will cause an alteration in the schizophrenic state." □