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SCHIZOPHRENIA AND THE BRAIN

Schizophrenia is a devastating disease of unknown cause. Its protean symptoms range from a pervasive blunting of affect, thought, and socialization, to florid hallucinations and delusions. Its characteristic onset during adolescence and young adulthood interferes with the most productive period of life and results in prolonged suffering. Even with the most up-to-date management, about half the patients have chronic deterioration, and the rest a more episodic course. The worldwide prevalence is approximately 1 percent. In the United States alone, the cost to society runs from $10 to $20 billion yearly.1

There have been two major advances in this field recently. First, the various editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association have introduced relatively objective criteria that have improved diagnostic uniformity. Second, dopamine-blocking neuroleptic drugs have vastly enhanced symptomatic relief, leading to a reduction in the rate of relapse and length of hospitalization. However, the diagnosis remains phenomologistic, and the treatment is palliative. Without a more fundamental understanding of the cause, it may not be possible to design a cure, prevent the disease, or find a specific diagnostic marker.

The quest for the cause of schizophrenia constitutes one of the most colorful chapters in the history of science. Stated in terms of a contemporary metaphor, a central question is whether the prime mover of this disease is in the software or the hardware — that is, does schizophrenia arise when a normally wired brain is subjected to schizophrenogenic programming, or does it arise because some fundamental miswiring precludes normal learning, including an adaptive response to stress? Studies in families and twins strongly suggest the existence of a genetic factor, but there is also evidence that psychological stress influences the timing of onset and relapse. Few investigators today would champion an exclusively psychogenic cause, and there is considerable agreement about the existence of a biologic factor. A major goal of current re-

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search is to elucidate the nature of the biologic factor (is it a gene, toxin, autoantibody, or virus?) and to decide whether it is the only determinant of the disease or whether its role is to provide an abnormal vulnerability to triggering factors that can in turn be biologic or psychological.

The search for a biologic factor is not new. Emil Kraepelin, who provided the modern description of schizophrenia almost a century ago, postulated the existence of central nervous system defects. His contemporaries described a number of neuropathologic abnormalities in the brains of patients with schizophrenia, but these were soon discredited as being either nonspecific or artifactual. Such criticisms and the success of the psychodynamic approach in many fields of mental illness pushed biologic research on schizophrenia into the background during the first half of this century. Psychodynamic psychiatry introduced a much more humane and psychologically sophisticated approach to patients with schizophrenia but did not offer substantial insights into the cause of the disorder.

Dramatic advances in all fields of basic and clinical neuroscience now provide a propitious environment for the resurgence of research on the biology of schizophrenia. The modern era in this field began with a focus on toxins and neurotransmitters. The triggering of schizophrenia-like symptoms by amphetamines (which have a dopaminergic effect) and the therapeutic effect of dopamine blockers (such as chlorpromazine) led to the hypothesis that schizophrenia may reflect a state of central dopaminergic excess. Despite a number of suggestive findings, however, there is currently no proof that either a neurotoxin or an abnormality of neurotransmission (including a dopaminergic abnormality) is a primary feature of schizophrenia. In the past two decades, the emphasis has shifted to the neuroanatomy and neurophysiology of the brain. Three areas have been investigated: regional neural activity, reflected by in vivo blood flow and metabolic rate measured with single photon emission computed tomography and positron-emission tomography; brain structure, studied in vivo with computed tomography and magnetic resonance imaging; and neuropathological characteristics of post-mortem tissue samples, as revealed by modern neurochemical and morphometric methods. Many of these studies have involved patients with longstanding disease who have also had prolonged exposure to medication. Conflicting results are common, but some trends are also emerging.

Regional metabolic activity in the brain of patients with schizophrenia displays a number of deviations from normal. Numerous studies have reported hypometabolism of the frontal lobe and various abnormalities of the temporal lobe, including hypermetabolism of the left temporal lobe. These findings have generated understandable enthusiasm, since the “negative” symptoms in schizophrenia (the blunting of motivation, affect, and thought) bear some similarity to the behavioral consequences of acquired frontal-lobe damage, whereas the “positive” symptoms (hallucinations and delusions) may emerge in patients with temporolimbic epilepsy, especially if the focus is left-sided. It is not clear, however, whether these deviant patterns of brain activity represent a cause or an effect of the disease or of medication. For example, patients who have never received medication have relative hypermetabolism of the frontal lobe rather than hypometabolism. Furthermore, hypermetabolism of the left temporal lobe seems to occur only if the patient is actively hallucinating, suggesting that patterns of regional brain activity may reflect ongoing behavioral states rather than primary abnormalities related to the etiologic process.

Neuroimaging research based on modern technological marvels such as computed tomography and magnetic resonance imaging has also detected deviations from the normal. The most consistent finding is an increase in the size of the cerebral ventricles (especially of the frontal and temporal horns) and a corresponding decrease in cerebral tissue, especially in medial temporolimbic structures such as the hippocampal complex. Studies in twins by Reveal et al. and by Suddath et al. in this issue of the Journal, provide nearly definitive evidence of the existence of such structural changes and also show that these represent, at least in part, an epigenetic or acquired phenomenon. The emphasis on the frontal and temporal lobes is in keeping with the findings emerging from studies of regional brain activity.

The neuroimaging studies raise a number of questions that remain unanswered. Does the increased ventricular size represent a failure of neural development or an acquired dissolution of brain substance? Is the ventricular enlargement ex vacuo (caused by the loss of surrounding tissue), or is it obstructive and therefore the cause of structural abnormality? Does it reflect changes primarily in gray or white matter, in cortex or basal ganglia? Is it intrinsic to the disease or merely due to psychological suffering and medications? Studies in animals, for example, have shown that the nature of experience can influence the thickness of the cerebral cortex and that some drugs can have exquisitely regional neurotoxic effects. Even the most convincing neuroimaging studies also indicate that the range of ventricular size in patients with schizophrenia overlaps considerably with that in nonschizophrenic controls. Not all patients with schizophrenia have abnormally large ventricles, and large ventricles can also be seen in different diagnostic entities ranging from manic depressive disease to Alzheimer’s disease. It appears that enlarged ventricular size is an intriguing but also indirect echo of some remote event in the brain of patients with schizophrenia. Since this finding is neither universally present nor specific to schizophrenia, its diagnostic value is understandably limited.

Neuropathological studies in schizophrenia have reported neuronal loss and aberrant architecture in the
cingulate gyrus and prefrontal cortex, gliosis in the basal limbic structures of the forebrain, and atrophy in temporolimbic structures such as the hippocampus and amygdala. One would have expected neuropathology to provide a gold standard for research on schizophrenia, but this is not yet so. The number of specimens that have been studied is small, the diagnosis is often retrospective, the medication status is frequently unknown, and many of the caveats and questions listed in conjunction with the neuroimaging research also apply to the neuropathological research. However, the brain sites implicated by neuropathological investigations do overlap substantially with those that have been implicated by neuroimaging studies.

These three lines of research indicate that not all is right in the brain of patients with schizophrenia. Schizophrenia is an immensely complex disorder in which sensorimotor functions and basic cognitive skills such as language and memory are relatively intact. The fundamental deficits occur in complex attention, volition, abstraction, inference, the integration of thought and perception with emotion, and the ability to maintain appropriate boundaries between internal and external reality. These behavioral domains are in keeping with the affilations of frontal and temporolimbic networks in the human brain, and it is interesting that these are also the two neural systems currently sharing the limelight of schizophrenia research. It could be argued that stroke, tumor, or trauma involving these areas does not result in a clinical picture identical to schizophrenia, but this may reflect the developmental or very early onset of the underlying process in schizophrenia, giving rise to a situation more reminiscent of miswiring or short-circuiting than of a total blackout.

It is currently impossible to distinguish primary pathophysiologic processes from secondary epiphenomena or idiosyncratic observations from those that are universal. Chances are that schizophrenia is a disease of the brain, but it is unlikely that such a complex, multifaceted, and fluctuating condition could be caused by fixed damage to a single brain site or neurotransmitter pathway. Studies of regional blood flow show that hypometabolism of the frontal lobe occurs when patients perform certain mental tasks but not others, suggesting that the deviation from the normal pattern might be dependent on context rather than fixed. Deviant left-right and frontal:parietal ratios of neural activity have also been reported, suggesting that there may be a state of imbalance among interconnected constituents of cerebral networks rather than a cessation of activity in any given component. Some of the neuropathological observations are consistent with disordered neural organization in the involved areas rather than a destructive process. These diverse observations suggest that the pathophysiologic mechanism may be based on a multifocal but partial distortion of neural processing, especially within frontal and temporolimbic networks. The nature of the lesion could be developmental, acquired early, or even intermittent and cumulative, as in epileptic or autoimmune disorders. Such a process could cause an early and context-dependent interference with the integrative function of frontal and temporolimbic networks, two neural systems known to subserve behavior at a level of complexity commensurate with that of schizophrenic symptoms.

Schizophrenia, as currently defined, is quite probably an umbrella term for several different diseases. Despite this formidable obstacle to valid research, observations in this field deserve to be taken seriously, since results that are initially difficult to reproduce may nonetheless contain clues to fundamental etiologic mechanisms, at least in certain subgroups of patients. The approach to schizophrenia research should therefore be cautious but not hypercritical, scientifically rigorous but also receptive to serendipity. The evidence strongly suggests that at least some patients with schizophrenia have detectable structural and physiologic abnormalities of the brain. Item E of the criteria for schizophrenia listed in the DSM (third edition, revised), the inability to establish an organic factor, may need to be eliminated. Perhaps this will start a trend toward the total elimination of the term “organic,” which is often a source of obfuscation and an obstacle to lucid differential diagnosis. The investigation and treatment of patients with schizophrenia may also encourage stronger collaboration between psychiatrists and neurologists, collaboration that may pave the way for a new neuropsychiatry based firmly on the neurobiologic principles of brain–behavior interactions.

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REFERENCES

FLUORIDE AND BONE — QUANTITY VERSUS QUALITY

Postmenopausal osteoporosis is a major public health problem, whose impact is expected to reach epidemic proportions during the early part of the next century as the population ages. Consequently, where as the prevention of bone loss will probably remain the most effective approach to therapy, efficacious treatment of patients who have already had fractures is sorely needed. The ideal therapy would eliminate the risk of future fractures by restoring bone mass and repairing the alterations in architecture that had already occurred. Current treatments such as those using estrogen and calcitonin are antiresorptive — that is, they act by preventing further loss of bone — but treatment with neither of those agents results in much net gain of bone mass or repair of bone structure. Great hope, therefore, has been placed on sodium fluoride, an agent known to increase bone density, especially in the spine. Unfortunately, the use of fluoride is often associated with side effects, including abnormalities of bone structure. Fluoride is incorporated into hydroxyapatite, altering the size and structure of the crystals and perhaps thereby decreasing the mechanical competence of the bone. When calcium intake is inadequate, the administration of fluoride also results in an impairment of mineralization. The bone formed in response to fluoride use may be somewhat disorganized, at least before remodeling, resembling immature woven bone rather than adult lamellar bone. Therefore, although the risk of fractures normally rises as the bone mass declines, increases in bone mass with fluoride treatment may not reduce fracture rates.

Until recently, there had been almost no well-controlled studies of the effects of fluoride in women with postmenopausal osteoporosis that used fracture frequency as an end point. In the early 1980s, with this in mind, the National Institutes of Health requested proposals for clinical studies of fluoride in the treatment of osteoporosis. The results of one such study appear in this issue of the Journal. The randomized, placebo-controlled, double-blind study of Riggs et al. was designed to determine whether sodium fluoride given at doses of 75 mg per day (60 mg and 90 mg on alternate days) would alter bone mass and reduce the rate of fractures over a four-year period in women with postmenopausal osteoporosis. Although bone density in the lumbar spine increased by approximately 35 percent in the fluoride-treated women, the overall rate of vertebral fractures did not decrease significantly, implying that the new bone was structurally unsound. These women had a smaller change in bone density in the femoral neck and a worsenome but not statistically significant increase in the rate of hip fractures. There has been a disputed suggestion that fluoride treatment increases the risk of hip fracture, and a surprisingly high frequency of such fractures among treated patients was found in one study. The increased number of peripheral fractures in the fluoride-treated group is equally disturbing. Although most were incomplete fractures, the relative risk for complete fractures was twice that in the placebo group. Besides the study’s failure to establish the efficacy of fluoride against fractures, there was a high incidence of side effects, primarily gastrointestinal distress and a pain syndrome of the lower extremities. Eleven of 19 patients with the latter problem had incomplete fractures at the site of pain, but the underlying cause of this syndrome in the others remains obscure. Unfortunately, the study did not include quantitative histologic data that might have aided the interpretation of the results, nor were the results compared in the women who had increased bone mass and those who did not.

The inescapable conclusion from this study is that sodium fluoride in the dosage used is not an effective or safe treatment for postmenopausal osteoporosis. The results were similar in a parallel but smaller study of similar design carried out at the Henry Ford Hospital in Detroit. Attempts to combine the data by using techniques of meta-analysis might be helpful in clarifying the findings that were not statistically significant in the two studies. Other studies have suggested that fluoride therapy is beneficial in postmenopausal women with osteoporosis, but a detailed review of the literature reveals mixed conclusions. Among recently published reports, a multicenter study conducted in France found no significant decrease in the occurrence of vertebral fractures in women treated with fluoride (50 mg per day as enteric-coated capsules) as compared with women treated with several standard regimens, but the probability of having a new fracture was significantly lower in the fluoride group according to survival analysis.

It is easy to find contentious issues in any clinical study of therapy for osteoporosis, and the several recent fluoride studies are no exception. The arguments will focus on the dosage, preparation, and duration of treatment. Other fluoride preparations, such as monofluorophosphate or slow-release capsules, or lower doses remain options for future investigation. However, it is important to note that the restoration of bone mass with fluoride, regardless of dose or preparation, cannot be taken as a surrogate measure for reduction of the fracture rate. Indeed, these studies raise the broader question of whether any therapeutic