THE SCHIZOPHRENIC BRAIN: REWRITING THE CHAPTER

With modern technology reviving a largely discarded research approach, the latest brain scan studies reveal structural abnormalities among the brains of persons diagnosed as schizophrenics

BY JOEL GREENBERG

Within the mysterious furrows and fissures of the brain's curious, claylike tissue lie the seeds of behavior and thought. And whatever day-to-day tribulations might contribute to the development of serious emotional disorders, many scientists are convinced that such problems ultimately are rooted in the brain itself.

Much current psychiatric thought suggests that schizophrenia — a rather confusing term used to define a collection of symptoms including loss of touch with reality, hallucinations, thought disorders and an outward lack of emotions — is intricately involved with (perhaps dictated by) the balance of brain chemicals. The disorder may be connected with a number of chemical systems, but the strongest evidence thus far indicates that some schizophrenics produce too much dopamine, one of several dozen identified transmitting substances that enable brain cells to communicate with each other (SN: 10/25/78, p. 362).

This neurochemical approach to psychiatric research is only about two decades old and breaks sharply with earlier work that focused on the search for *structural* abnormalities in the brains of the emotionally disturbed. Some of these studies during the first half of the century reported the existence of enlarged cerebral ventricles (cavities) and other physical problems in the brains of schizophrenics. But those studies were plagued by poor research designs and technology of questionable reliability; the process of pneumoencephalography — which consisted of injecting air or gas into brain cavities to enable X-ray of such areas — was painful, and could have caused the ventricles to expand in some cases. After subsequent studies on the brains of deceased schizophrenics failed to confirm ventricular enlargement, biological psychiatry turned toward the relatively untapped field of neurochemistry.

Now, however, some researchers are warning that the pendulum may be swinging too far toward brain chemistry, and that their colleagues must not ignore other possible contributors to mental illness — such as environment and the largely discarded possibility of brain structure abnormalities. What has primarily rekindled hope among structural investigators is the advent of computed tomography (CT), or computerized axial tomography (CAT) — a painless and precise technique of scanning living brains.

And to the surprise of more than a few observers, the latest, more sophisticated studies are tending to confirm the findings of some earlier, primitive work: that certain schizophrenics do indeed appear to have significantly larger cerebral ventricles and other abnormalities (albeit subtle ones) not found in the brains of "normal" persons. Several recent research results, presented at the annual meeting of the American Psychiatric Association, offer some of the strongest evidence yet that certain types of schizophrenia may be linked to slight but significant deviations in brain structure.

"In light of these CT scan findings and the current conception that schizophrenia is not a single disease entity [but possibly a collection of bits and pieces of various abnormalities], the chapter on neuropathology and schizophrenia may need to be rewritten," says psychiatrist Daniel R. Weinberger of the National Institute of Mental Health's Laboratory of Clinical Psychopharmacology. "We've found a very strong association between chronic schizophrenia and structural abnormalities." Weinberger and his colleagues report that among more than 80 psychiatric patients they have examined with CT scans, "approximately two-thirds of the chronic schizophrenics have some structural abnormalities." (Chronic schizophrenics — as opposed to shorter-term, acute patients — are defined as persons psychotically ill for more than one year, or who have not fully recovered from a previous psychotic episode.)

Chief, but not solitary, among structural problems is the enlargement of ventricles. Among 63 chronic schizophrenics examined, 40 percent had ventricles larger than *any* of the 64 normal control group members, and more than half the schizophrenics had ventricles larger than 95 percent of the controls. While the enlargements were not nearly as marked as those seen in senile and presenile dementia patients, the ventricle sizes in the affected schizophrenics — who had a mean age of 30 years — were "the same as people 40 years older," says Weinberger, who conducted the research with NIMH's Richard Jed Wyatt and E. Fuller Torrey and New York University's Andreas N. Neophytides.

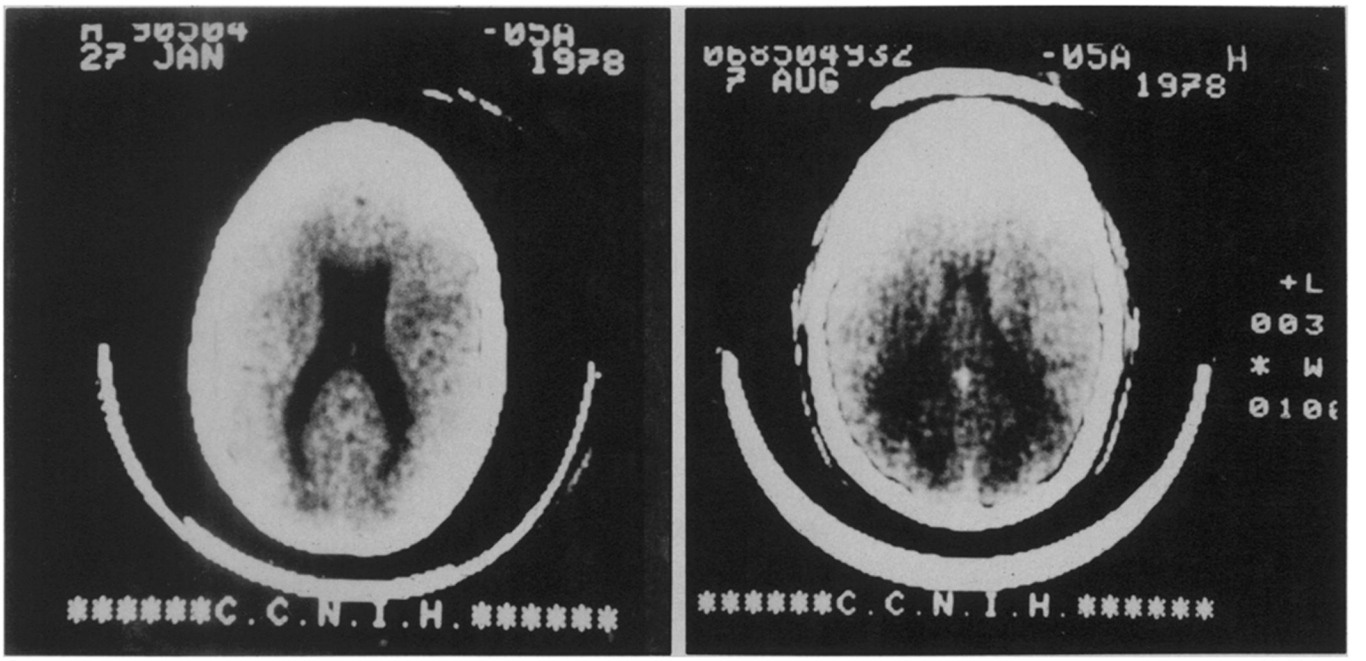
Because most of the schizophrenic enlargements are subtle to the eye, perhaps not even noticeable at a routine glance, the investigators performed up to a dozen scans on each person and meticulously calculated the ratio of the ventricles to total brain size — a computation previously shown to correlate with computer estimates of ventricular volume.

But what could cause these brain cavities to apparently age prematurely, to expand, as they did in the case of one 23-year-old male patient, to as much as six times normal size? According to the NIMH study, the condition does *not* result from electric shock treatments, alcohol or drug consumption, length of illness or length of institutional treatment. The enlarged ventricles, Weinberger says, represent "mild cerebral atrophy that is not apparently progressive and correlates only with the occurrence of chronic schizophrenia."

While such abnormalities "may not be typical of all patients with the diagnosis of chronic schizophrenia ... these studies demonstrate to us that structural brain abnormalities are associated with schizophrenia," he says. Even among chronic schizophrenic patients whose ventricles may fall within normal range, researchers are beginning to discover other brain abnormalities.

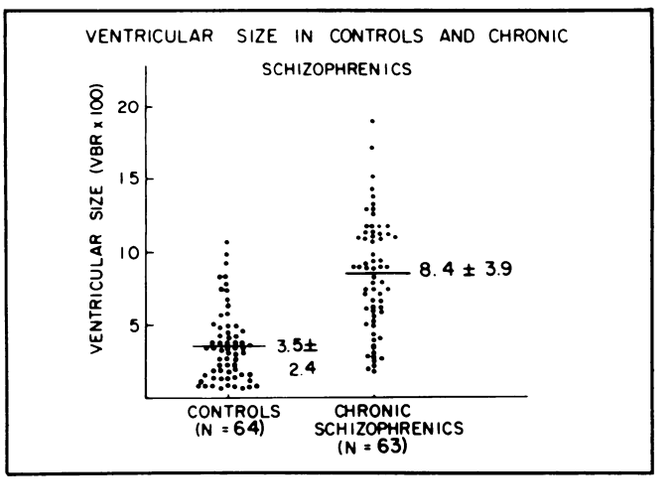
NIMH's Daniel J. Luchins, along with Weinberger and Wyatt, reports that in a surprising number of schizophrenics, brain hemisphere sizes appear to be reversed — almost mirror-images of normal brain structure. CT scans have previously shown that normal, right-handed individuals tend to have wider right frontal and left occipital (located in the rear of the brain) lobes, according to Luchins. Reversals of "normal" occipital asymmetry have already been reported in children with autism, delayed speech onset, developmental dyslexia and poor verbal performance. Enough clinical reports of possible asymmetry-related behavior problems among schizophrenics — including a tendency toward "left-handedness" — had surfaced to prompt Luchins and his colleagues to examine the physical brain structures of 57 right-handed schizophrenic patients.

They found that one-third of these patients exhibited frontal lobe size reversals and one-fourth showed occipital lobe reversals. Among the 80 normal CT scan studies, only 13 percent had frontal, and 7 percent occipital, reversals. Perhaps more



Photos: Daniel R. Weinberger/NIMH

Computed tomography scans show the shaded, tong-shaped ventricles in the brain of a 36-year-old schizophrenic woman (left) are noticeably larger than those observed in the brain of a 25-year-old nonschizophrenic man.



Statistical distribution demonstrates that the cerebral ventricles of normals are significantly smaller than those of chronic schizophrenics, 40 percent of whom had ventricles larger than even the largest among the control group.

significant, among schizophrenics *without* signs of some sort of brain atrophy, the reversal figures jumped to 52 percent for frontal and 38 percent for occipital. Luchins also reports that patients with frontal lobe reversal alone tend to have milder, shorter-term schizophrenia than those with just occipital or both types of reversals.

Along with such reversed asymmetries — which, Luchins says "seem to occur early in life, perhaps in the embryo" — come reports of other possible structural deviancies in schizophrenia. Henry A. Nasrallah of the University of California at San Diego has studied the preserved brains of 64 St. Elizabeth's Hospital patients with various disorders who died between 1972 and 1977. He reports that the corpus callosum — one of several structures connecting the left and right hemispheres — tends to be thicker in early onset than in late onset schizophrenia. In many cases, the earlier a person is stricken with schizophrenic symptoms, the poorer the prognosis, says Nasrallah.

These results suggest that abnormal communication between brain halves could at least partially account for common schizophrenic characteristics such as short-term memory problems, thought disorder, emotional flatness and blocking. Such symptoms, along with ambivalence, "may be the result of two 'separate minds' in schizophrenics," says Nasrallah.

In another study — this one by Laurence Schweitzer of the Baylor College of Medicine — 13 schizophrenics and 13 psychotically depressed patients underwent a series of tests designed to reflect use of either brain hemisphere. The results indicate that schizophrenia may be associated with "a left hemisphere ... disturbance" and that "psychotic depressive pathology may be associated with increased right hemisphere activity," says Schweitzer.

Finally, Weinberger has also found that in some schizophrenic brains, the interhemispheric "Sylvian" fissure and certain cortical trenches, or sulci, are significantly wider than in normal brains; and parts of the cerebellar vermis — a wormlike structure between the two brain halves — is stricken with atrophy. "A growing body of basic science research indicates that the cerebellar vermis is linked anatomically and functionally to areas of the limbic system [part of the brain thought to regulate emotions] that have been implicated in schizophrenia," Weinberger says. Furthermore, increased dopamine production in the limbic system — the major tenet of the "dopamine hypothesis" of the cause of schizophrenia — has been produced in rats by inflicting a lesion, or tiny injury, to the vermis.

This last result provides one demonstration that the structural abnormality approach to schizophrenia research "is not opposed at all" to the neurochemical approach, Weinberger says. "Structure and chemistry are not divisible events in biology. All structural disorders cause biochemical changes and vice versa — Huntington's disease, Alzheimer's and others [structural problems] have a chemical impact, while diabetes, among other [chemical disorders] can affect the lungs, kidneys... even the brain," he says. "These things are related; it would be bizarre if they weren't."

Still, Weinberger says that the overriding emphasis on brain chemistry — as opposed to structure — over the past decade or more has "restricted our view to neurochemical aspects." But though the clinical significance of these latest findings concerning brain structure abnormalities is "still unclear," Weinberger believes their eventual impact will be considerable. The NIMH work, he says, already "challenges the widely held belief that structural brain abnormalities do not occur in schizophrenia." □