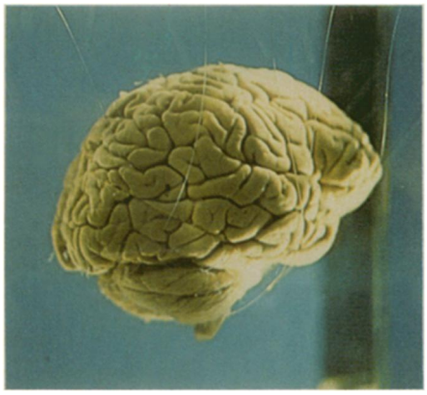


THE BRAIN
Holding the Secrets of Behavior

The brain's neurochemical networks are yielding promising clues to schizophrenia, depression and other emotional problems

BY JOEL GREENBERG

It starts with a tiny "spark." A nerve impulse sizzles its way along a cell's fuse, the axon. The journey ends with a mini-explosion, in which splashes of chemical neurotransmitter — the suspected fertilizer of our thoughts, ideas and feelings — are spewed from the cell across a synapse, or connecting gap. A nearby nerve cell captures and coexists with the transmitter through the next critical period of its work. Other cells ignore the substance, allowing roaming enzymes to break down parts of it, or an original releasing cell to scavenge it for future ammunition.

This process continues at varying degrees among billions of brain cells, or neurons, throughout life — day and night (though to a lesser extent during sleep); in the genius and the "slow learner"; in the emotionally disturbed and the "normal."

The workings of this complex machinery are far from random. In fact, many behavioral scientists and neuroscientists now believe that much of the brain's activity is preprogramed and that some unknown portion of it is genetically determined. Although environment — upbringing, surroundings and interpersonal relationships — is still believed to influence emotions to an extent, some researchers are placing growing emphasis and responsibility for behavior on the neurochemical and structural components of the brain. (There remain, however, a significant number of behavioral scientists committed to the idea that environment is the driving force in mental processes.)

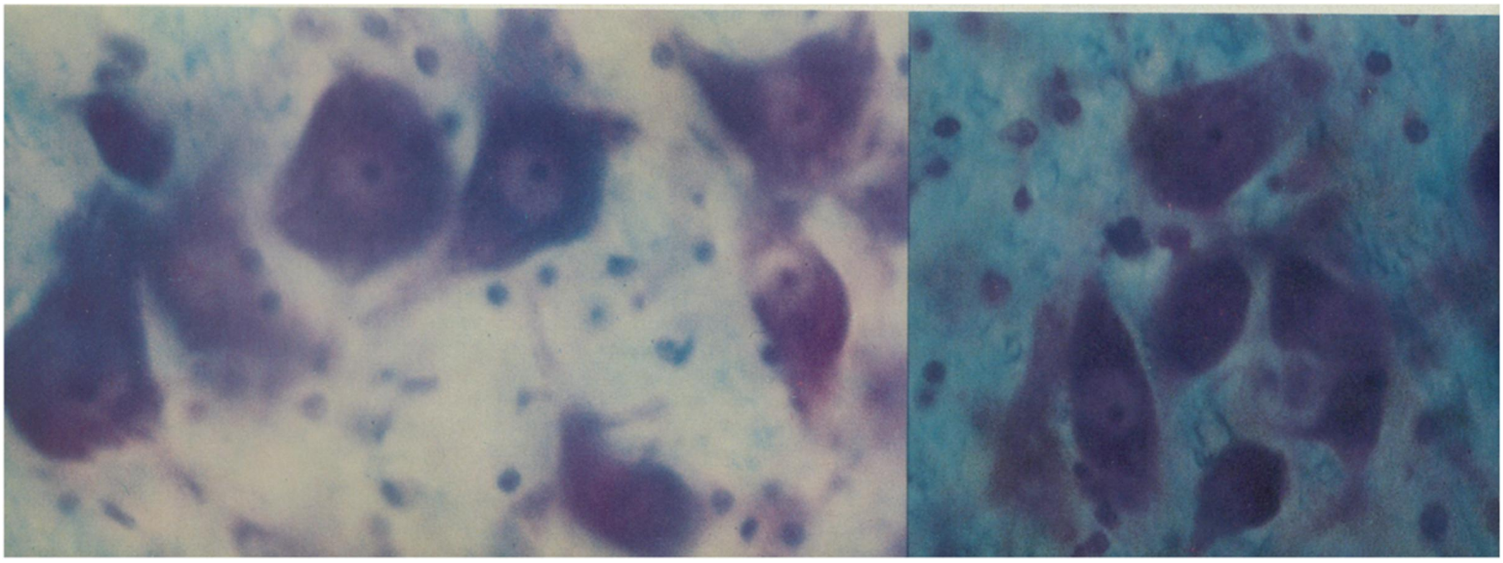
"All decisions of the brain in the end basically have to do with the 'decision' of whether a neuron will fire or not," contends psychopharmacologist Larry Stein of Wyeth Laboratories in Radnor, Pa. Most behaviors, however, do not result from the firing of a single neuron, but from the orchestrated flow of intertwining chemical rivers that branch through various areas of the brain.

And while knowledge of neurotransmitter systems is growing rapidly — nearly 40 transmitters have been discovered, most within the past two decades — it is coming at almost too fast a rate for behavioral scientists to digest. "All these chemical transmitters are being released onto their receptors, which either excite or inhibit the neuron ... that's basically how the brain works," Stein says. "What we have to figure out now is how all these systems are organized."

Perhaps nowhere is the impact of this avalanche of knowledge being felt more heavily than in the understanding and treatment of serious emotional disorders, such as schizophrenia and depression. On the one hand, Harvard University neurophysiologist Seymour Kety "see[s] psychiatry as having finally become a scientific discipline, with opportunities to learn about the pathological process; with opportunities to develop better diagnostic tools, better understanding of the basic mechanisms of disease, better understanding of the pharmacology of treatments ... than it's ever had before." On the other hand, Frederick K. Goodwin of the National Institute of Mental Health says, "The understanding of the brain has not yet given way to any new treatments ... most of the known treatments in psychiatry have been accidental observations."

But if accidental in origin, many drug treatments for schizophrenia and depression are being at least partially vindicated and confirmed by new knowledge of the brain. "If what we've found [about schizophrenia] is true, then we know that clinicians have been giving the right drugs, to an extent — but a lot more has to be learned," says Edward D. Bird, who recently joined McLean Hospital's Mailman Research Center in Belmont, Mass., which Kety directs.

Since the first use of a neuroleptic, or antischizophrenic substance, with patients in 1952 (this was indeed an "accident," because the first such drug, chlorpromazine, was expected merely to sedate hyperactive patients), researchers have found that those drugs perform one consistent chemical action in the brain: They appear to block cell receptor sites that are activated by the neurotransmitter dopa-



mine. Along with its first cousin, norepinephrine, dopamine is classified in the catecholamine family and has been implicated, along with other transmitters, as a major factor in various behavioral states.

But dopamine's starring role seems to be in schizophrenia — itself a confusing, pervasive condition that psychiatrists have trouble defining, let alone treating (SN: 9/30/78, p. 230). Nevertheless, there is a growing consensus that schizophrenia is probably a "collection" of brain malfunctions that cause a serious emotional disability, which — despite drug treatment — can affect a person for the majority of his or her life. "I don't think that all schizophrenia is caused by the same brain disease," says Steven Matthysse, a psychobiologist at the Mailman Center. "It's probably a group of brain diseases — and when I say 'brain disease,' I'm prepared to believe that.... I'd be surprised if family environment made the slightest difference [in schizophrenia]."

Because so many major investigators share Matthysse's disease-oriented view of the ailment, most current research in schizophrenia centers on brain neurochemistry. Among the latest and most compelling evidence that dopamine is involved in schizophrenia are Bird's findings with autopsies of brains of deceased, chronic schizophrenics. A pioneer in autopsy brain analysis of Huntington's chorea, Bird began studying schizophrenic brains two years ago while at Cambridge University in England. "Many patients admitted to hospitals with a diagnosis of schizophrenia later were found to really have Huntington's disease," says Bird, who is starting a "brain bank" at the Mailman Center. "I felt I should look at schizophrenic brains because there probably is a final common pathway for neurochemical changes that may well be very similar to Huntington's disease."

Now, after using radioactive isotopes to examine 75 brains of schizophrenics, Bird has found that, like Huntington's victims, schizophrenics have a significant excess of dopamine in their brains — about 50 percent more than that in nonschizophrenic brains. What makes the findings particularly intriguing is that the dopamine overproduction is found almost exclusively in the brain's limbic system, which is thought to regulate emotional behavior. No excess has been found in the basal ganglia, a brain center mediating physical movement — an area where, in Huntington's disease, dopamine appears to flow out of control, leaving visible signs of tissue destruction. But though schizophrenic brains look anatomically normal, Bird's work is among the first to confirm by direct measurement in human brains previous results with animals and indirect measurements of neuroleptic actions — most pointing to a distinct overactivity of dopamine in the limbic system that may be alleviated by administration of drugs that block dopamine receptors. Similar post-mortem brain studies by the University of Toronto's Philip Seeman indicate that schizophrenics have about twice the normal number of dopamine receptors (SN: 11/19/77, p. 342).

Unfortunately, this evidence, though promising, is still far too preliminary and incomplete to enable researchers to solve the entire puzzle of schizophrenia. For one thing — and Bird is the first to note this — elevated dopamine levels in the brains of chronic schizophrenics may be due at least partially not to a disease factor but to long-term use of antischizophrenic drugs. By blocking dopamine receptor cells, neuroleptic drugs actually seem to stimulate dopamine production in the "pre-synaptic" or releasing cells. "The brain has an incredible capacity for adaptive and redundant mechanisms," says Goodwin, chief of NIMH's clinical psychobiology branch. "If you have blockage of these transmitters with a drug ... these mechanisms will try to increase synthesis of the transmitter to overcome the blockade."

But Bird says there is one aspect of his autopsy results that indicates excess dopamine is pathological, rather than merely a drug byproduct, in schizophrenia: No such excess is found in the basal ganglia of schizophrenics, where dopamine occurs at an even higher rate than in the limbic system, and where receptors are also blocked by neuroleptics (which seek out dopamine receptors throughout the brain). This suggests that there may be a factor intrinsic to the limbic system that relates to dopamine hyperactivity and schizophrenia, he says.

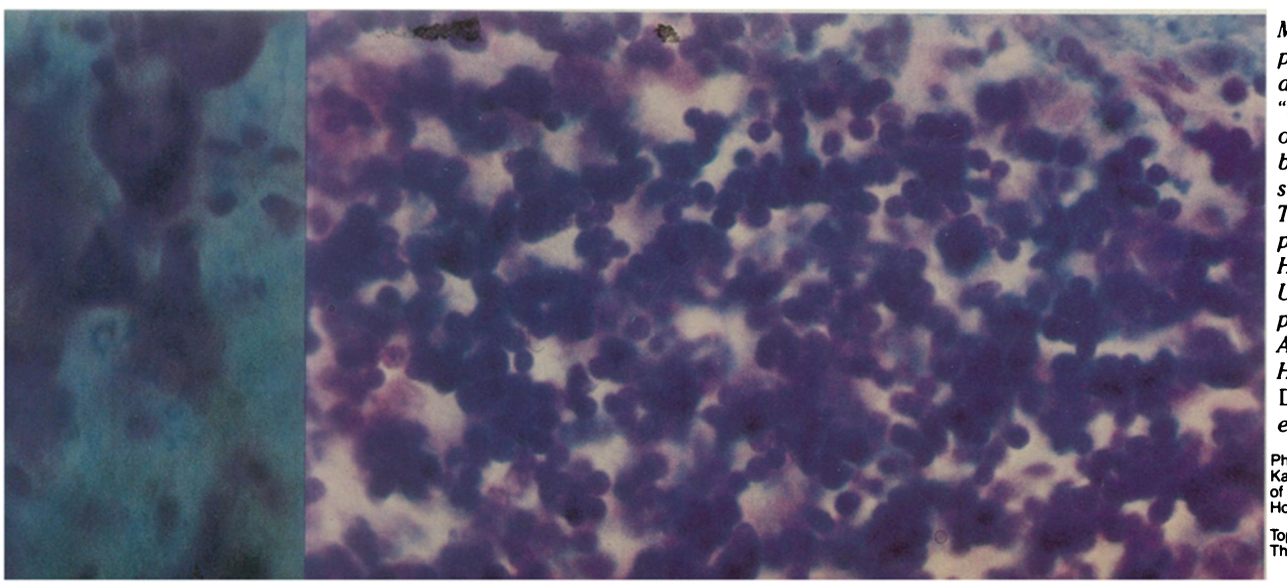
Still, there remains one inescapable factor that casts considerable doubt on the role of dopamine in schizophrenia: Neuroleptic drugs, while helpful in alleviating some symptoms, fail to stop the overall deterioration of many chronic, severe schizophrenics. "The patients' agitation and intensity of thought disorder *do* diminish with antipsychotic drugs," Matthysse says. "But actually the delusions don't go away. Drugs also do very little for motivation — it's a sad thing, but a schizophrenic is very rarely motivated to do anything. And the drugs do very little for interpersonal relations." Goodwin concurs: "The long-term process of withdrawal; the flatness and dullness; the lack of interest that begin early in life — no one's found any way to stop that process."

Perhaps most exasperated and puzzled over the failings of neuroleptic drugs is Bird. "I just don't understand why these people don't come back to normal," he says. "I think it may be an irreversible biochemical change in the brain ... I don't know ... it's a problem."

All of this demonstrates that while certain dopamine characteristics may serve as a signal of schizophrenia, study results "have by no means demonstrated that the brain in that disease involves dopamine itself," says Soloman H. Snyder, distinguished service professor of psychiatry and pharmacology at Johns Hopkins University. "The fact that a dangerous short circuit can be abolished by tripping the appropriate circuit breaker does not mean that the short is in the breaker — it may be anywhere in the circuit ... the therapeutic action of neuroleptics [does] not necessarily mean that dopamine synapses are disturbed in schizophrenia."

What else, then, might contribute to schizophrenia? There are preliminary indications from Snyder, Bird and others that some defect might exist in the brain's enzymatic systems, which are supposed to break down or inhibit excess dopamine. Such enzymes include MAO (monoamine oxidase) and glutamic acid decarbox-

Continued on page 366



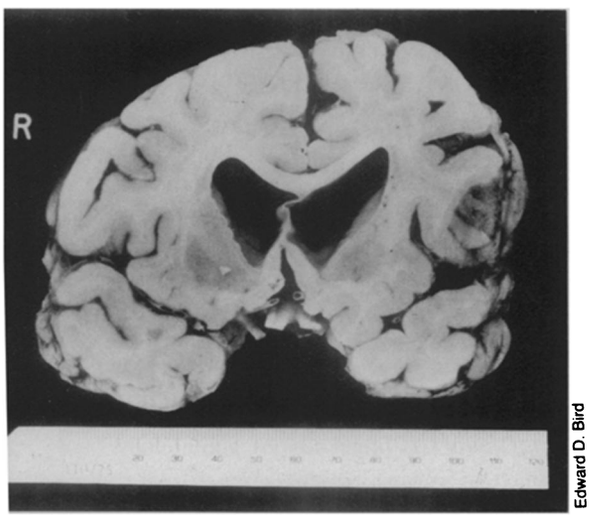
Microscopic projections depict the "landscapes" of various brain cell structures. The slides are part of Harvard University psychiatrist J. Allan Hobson's Dreamstage *exhibit.*

Photos: Ragnhild Karlstrom, courtesy of J. Allan Hobson and Hoffman-LaRoche, Inc.

Top photo by Theodore Spagna.

ylase, which manufactures GABA (gamma aminobutyric acid), a substance known to inhibit the production of dopamine and other neurotransmitters in the brain. Snyder also suggests that the uptake systems in dopamine-manufacturing cells of schizophrenics may be faulty in their ability to retrieve transmitter material that does not bind to a receptor neuron. And some preliminary studies have implicated norepinephrine in schizophrenia as well.

In addition, Matthysse is starting to search for possible *anatomical* malformation in dendrites, the outgoing branches of neurons. On the surface, such research might appear to be a step backward, because the "revolution" in brain study over the last decade has focused on chemical neurotransmitter systems and moved away from the concept that specific mental disturbances were concentrated in individual regions of the brain. But as more has been learned about transmitter systems, the more apparent it has become that many act in ways peculiar to the brain region in which they are located (for example, dopamine functions differently in the limbic region than it does in the ganglia). "You can't catalogue the importance of [transmitter] systems by simply counting the numbers of neurons," Goodwin says. "Not only are transmitter receptors localized in specific places, in specific patterns, but there may be multiple types of receptors for the same substance."



Edward D. Bird

Disproportionately large ventricle areas (black portion in center) reflect cell loss in brain of a Huntington's victim. No such loss is visible in schizophrenics.

Many investigators now believe that behavioral states ultimately will be traced to both neurochemical and physical systems in the brain. "I would assume that if there is a pathology, it would be simultaneously anatomical and chemical," says Matthysse. He believes that a dendrite may "show sort of a living record of its own history [that] reflects its metabolic environment as it grew up, just as the branches of a tree do." The dendrites of animals with brain disease are often malformed dramatically — like "a weeping willow structure," he notes. "We think that is one of the things that might happen in mental and neurological diseases.... There might be some changes in the degree in the organization of the cells."

Whatever the eventual causes, many researchers are convinced that serious emotional problems have a strong genetic component. Kety's studies of biological families of adoptees in Denmark strongly suggest that schizophrenia may be largely inherited (and he speculates that those cases that are not genetic may be due to a virus of some sort) (SN: 10/7/78, p. 244).

The same research, along with investigations of the behavior of twins, also indicates that genetics may play nearly as great a role in a person's susceptibility to serious depression and to suicide. This is an area in which environmental and psychosocial factors are believed to have substantial influence. However, there is growing suspicion that, like schizophrenia, serious depression — and its opposite, mania — may have a neurochemical basis.

"Is it possible for someone to wind up... seriously, pathologically... depressed because society makes them depressed? I don't think so," says Stein. "The normal brain is damned adaptive ... it may undergo a short-term, adaptive depression when things are going bad, but it bounces back." He suggests that "the depressive is suffering from the biology of his 'good feeling machinery.'" (See p. 364.)

Stein, Goodwin and others seem to have had somewhat better luck deciphering and treating the machinery of depression than researchers have had with schizophrenia. The tricyclic antidepressant drugs work to "balance" a number of transmitter systems, primarily norepinephrine, serotonin (an "amine," or slightly altered amino acid transmitter) and perhaps dopamine. Other drugs that have had some success in helping depression are the MAO inhibitors, which, as the name implies, help stimulate production of various transmitters in the brain by blocking MAO enzyme, which normally inhibits the release of those transmitters.

Goodwin suggests that various types of tricyclics, or the MAO inhibitors, work for some people but not for others because neither depression nor schizophrenia is a uniform phenomenon. "It may be that what happens in some of these illnesses is that their regulatory mechanisms are out of whack," he says. Persons with low-functioning serotonin neurons respond well to serotonin-active antidepressants, and a similar rule applies when administering norepinephrin-active substances to persons with low levels of that transmitter. But sometimes a paradoxical drug reaction — such as giving a stimulating amphetamine to a schizophrenic — will "knock" the system back into balance.

Direct, accurate measurement of such brain transmitter activity in living humans has, of course, been difficult — blood, urine and even cerebrospinal fluid measurements have provided questionable reflections of brain dynamics. For this reason antidepressive drug treatment often is a "hit or miss" proposition until a psychiatrist finds the drug that seems to help a particular patient. (The progression usually begins with tricyclics and, if those fail, moves on to MAO inhibitors and, in severe cases, electroshock — on which Snyder comments, "I can assure you, if you hook up someone to a house current, it's going to affect the whole brain — but where? how?") (See p. 359.)

In this less-than-foolproof procedure, administering a certain drug to a particular patient occasionally is "like using a Mack truck to shift a flower," as one psychiatrist describes it.

Now, however, Goodwin and his colleagues have developed improved methods of studying neurotransmitter metabolites in the blood, urine and spinal fluid. The new method appears to be able to "correlate changes in receptor functions with receptor changes," Goodwin says. Using a technique called negative ionization, the researchers have already measured metabolites of norepinephrine and serotonin in studies of human aggression (SN: 6/3/78, p. 356), depression and mania (see p. 367).

This, along with other recently developed techniques in brain research, has "opened up a brand new way of looking at the brain in living people" and promises to help identify additional neurotransmitters, Goodwin says. The recent discovery of the brain's "natural opiates" — endorphins and enkephalins — is already being applied to behavioral treatments and philosophies (see p. 374). And Goodwin's lab, among others, is tracking what some feel is a naturally occurring valium-type substance in the brain. (This work has resulted from the discovery by R. F. Squires in Copenhagen that radio-labeled valium binds to "highly specific" receptor sites in animal brains.)

At the moment, however, most behavioral researchers concede that the state of knowledge about the brain and behavior — though far more advanced than ever before — is still in its relative infancy. The long-term effects of some neuroleptics remain a mystery — for example, tardive dyskinesia (uncontrollable twitching of the face and extremities) remains a common side effect of antipsychotic drug use.

"The brain is a heck of a lot more complicated than any other organ in the body," says Kety. "Some day it may be possible to get a treatment that is so specific it eradicates the *cause* — then you have a cure." He suggests that such knowledge might even lead to prevention of emotional disabilities. But knowledge of a specific cause, Matthysse says, does not assure prevention. "At the moment," he says of a hypothetical cause of schizophrenia, "we wouldn't know what to do if we found it." □