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# Drugs and the Brain

by HENRY A. LESTER

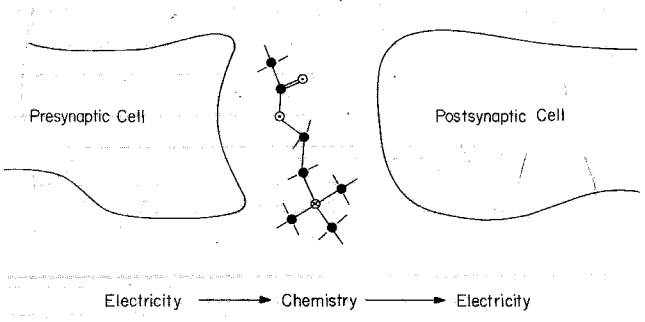
A Caltech neurobiologist discusses how some well-known drugs act upon the billions of nerve cells in the human brain

There are several useful definitions of a drug. It might, for instance, be the stuff obtainable from a pharmacist with a prescription from a physician. Or it might be something psychoactive, capable of influencing thought, perception, or behavior. These days, biologists have a rather general definition of a drug as any substance that affects the function of a living cell. In the spirit of this definition, we can identify thousands of drugs that we encounter or hear about in our society.

Here we are particularly interested in drugs that affect nerve cells. Most of the human body's ten billion or so nerve cells are found in the brain; and in the brain are located cells influenced by drugs such as Valium, strychnine, caffeine, L-DOPA, cocaine, Elavil, morphine, and of course LSD. Neurobiologists spend a good fraction of their time tracking down mechanisms of drug action, both because of the enormous therapeutic potential and because of the fascinating details that such investigations reveal about the way the nervous system functions.

Nerve cells have one predominant role — communication. They receive signals from the outside world; such signals become perceptions. They send signals to the outside world; such signals become the motion of muscles. And they communicate with each other. Indeed, most nerve cells in the brain just communicate with each other, elaborating and analyzing the signals to and from the external world. The language of this communication is the nerve impulse, a brief electrical event that travels throughout the branches of the nerve cell. All nerve cells in all animals apparently produce very similar impulses, lasting from one to ten milliseconds and measuring about a tenth of a volt in amplitude. How can this rather simple, brief electrical impulse, this universal code of the nervous system, allow the brain to perform all its diverse functions — perception, control of motion, emotion, cognition, the dance of the honeybees, the migration of birds? And how is this basically electrical code so sensitive to outside chemical influence?

The answer to both of these questions lies largely in the events that allow nerve impulses to travel between individual nerve cells and between groups of nerve cells. These events, which fascinate many modern neurobiologists, occur at a structure called the synapse, from the Greek for *contact*. In a highly schematic view of a synapse, there are two cells, the transmitting or *presynaptic* cell and the receiving or *postsynaptic* cell. When the impulse arrives at the synapse, it liberates a chemical substance called a transmitter. The transmitter then acts on the postsynaptic cell and reinitiates the electrical impulse. Thus, there is a chemical step in the hop that takes the impulse from one cell to another. It is because of this chemical step, and because this step occurs in the space between two nerve cells, that synaptic transmission is so highly susceptible to outside chemical influence.



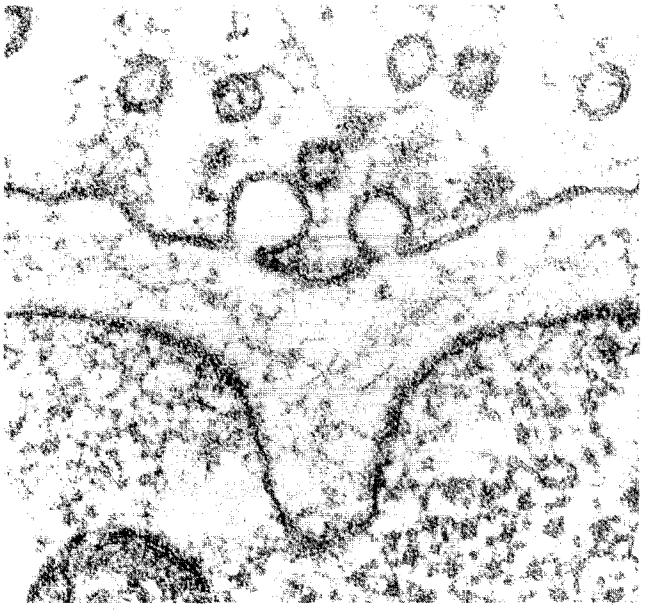

At the synapse, a chemical step transmits the electrical impulse from the presynaptic, or transmitting, nerve cell to the postsynaptic, or receiving, cell. The diagram above shows this step occurring via an acetylcholine molecule at the nerve-muscle synapse. In actuality, the molecule is much smaller relative to the nerve cells, and many such molecules participate at a single synapse.

There are dozens, perhaps hundreds, of transmitter substances in the brain and elsewhere in the nervous system. Each of these natural transmitters is associated with a constellation of drugs — some found naturally in the body, but most not — that modify synaptic transmission. Each synapse has only one transmitter, and a typical cell in the brain might receive signals at thousands or tens of thousands of synapses. Such a cell might, in turn, send signals to other nerve cells at other thousands of synapses. The brain may therefore be viewed as a network of nerve cells signaling each other chemically at synapses.

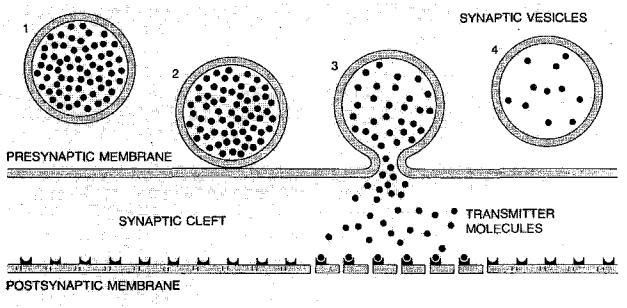
Imagine the path taken by a train of impulses that command a finger to move. The impulses arise in the brain, hop one or two synapses to reach the spinal cord, and hop one or two more synapses to reach the nerve that serves the arm and hand. One synapse remains — that between the nerve and muscle cells that move the finger. This nerve-muscle synapse, the last link in voluntary motion, is quite accessible to study. Neurobiologists now know a great deal about this synapse, and it serves as a reference point or model for other research on synapses. In some ways, the nerve-muscle synapse is the *E. coli* of neurobiology.

The preparations for synaptic transmission begin well before the impulse reaches the nerve-muscle synapse. The nerve (the presynaptic cell) is constantly packaging molecules of its transmitter, acetylcholine, into vesicles. The vesicles have a diameter of about 500 Angstroms, and each contains about 10,000 transmitter molecules plus a few other chemical species whose function still puzzles us. When the nerve impulse arrives at the synapse, a pulse of calcium apparently enters the nerve cell from the external fluid — essentially filtered blood — that bathes most of

Micrograph by John E. Heuser of the University of California School of Medicine in San Francisco.



This electron micrograph shows a synapse frozen by liquid helium at the moment the impulse arrives. Two synaptic vesicles, already fused to the presynaptic membrane are liberating their acetylcholine molecules into the space between nerve and muscle cells (center horizontal band). Other vesicles can be seen in the presynaptic (nerve) cell, which stretches across the top; the postsynaptic (muscle) cell is at the bottom. A schematic view of the electron micrograph (below) also shows the transmitter molecules binding to the receptors in the postsynaptic membrane.




From "The Neuron" by Charles F. Stevens. Copyright September 1979 by Scientific American, Inc. All rights reserved.

the body's cells. Within less than a millisecond, the calcium in turn causes some of the vesicles to fuse with the presynaptic membrane. The vesicles then liberate their transmitter molecules into the space between the nerve and the muscle.

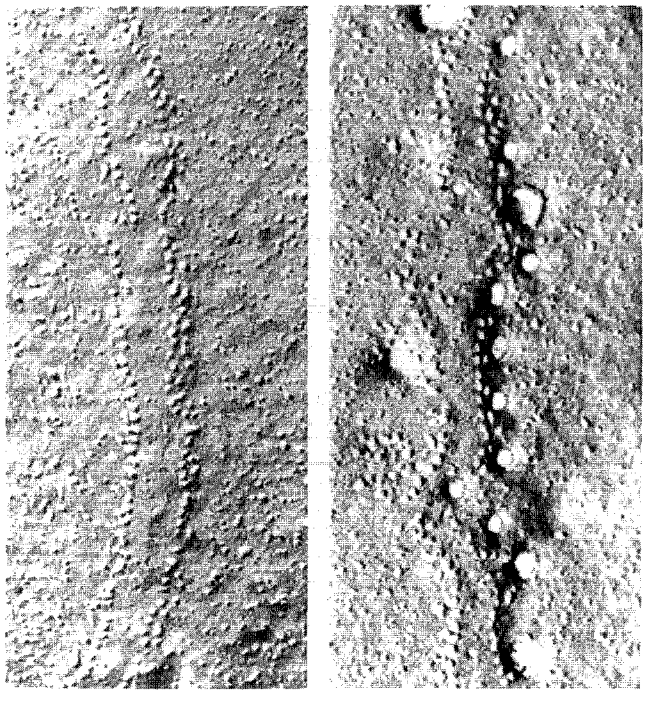
Some potent drugs interfere with the process of transmitter release. Botulism, one type of food poisoning, is caused by a bacterial toxin that apparently prevents the fu-

sion between vesicles and the presynaptic membrane. Transmitter is not released; the impulses never reach the muscle; and paralysis results. A complementary situation arises through the action of the black widow spider's venom. In this case, an "avalanche" of synaptic vesicles fuses with the membrane of the presynaptic cell; too much transmitter is released; and the spider's prey suffers muscular spasms.

Once liberated from the presynaptic nerve cell, acetylcholine molecules probably require only a few microseconds to diffuse the 500 Angstroms or so to the membrane of the postsynaptic cell. Next, the transmitter molecules interact with special proteins embedded within this membrane at the synapse but nowhere else in the normal cell. These proteins, called receptors, are packed so tightly that there seems to be little room for other structures in the membrane. The receptors function to reconvert the chemical message back into an electrical one.

According to present concepts, each receptor molecule

Micrograph by John E. Heuser.



These electron micrographs show the presynaptic membrane as seen from outside the cell. In the view on the left, the synapse has been frozen without an impulse while the synapse on the right shows the membrane at the moment the impulse arrives. The white globs in the right-hand picture are the vesicles fused to the membrane, liberating their contents of transmitter molecules. The smaller bumps visible in both views, membrane particles, may be sites where the inward pulse of calcium flows to trigger the fusion.

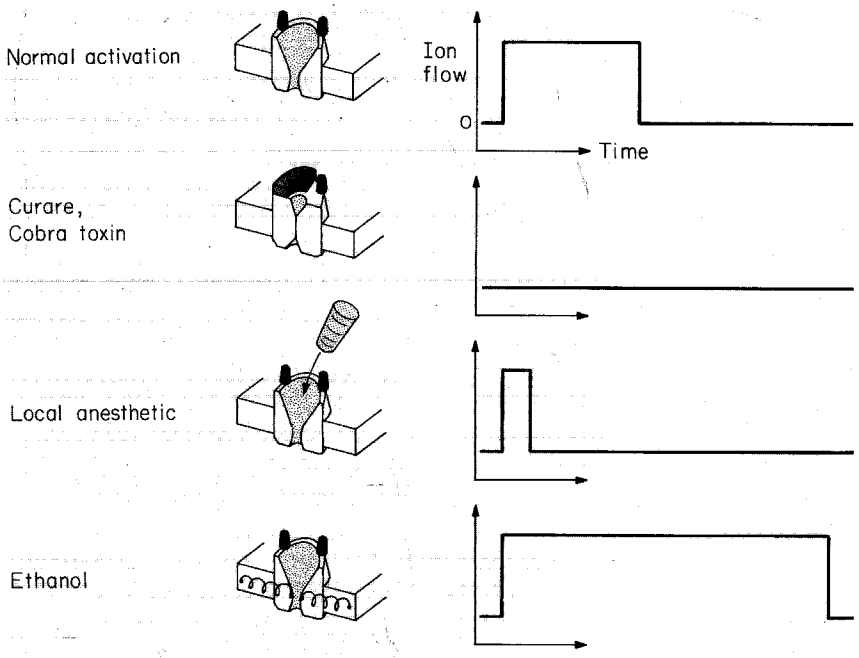
seems to guard a pore, or "channel," in the postsynaptic membrane. The pore opens if — and only if — two molecules of acetylcholine bind to one receptor molecule. The open channel seems to be a few Angstroms in diameter, and it allows ions (charged atoms) of sodium and potassium to flow in and out of the cell. The flow consists mainly of sodium ions, and its predominant direction is inward. This flow of positively charged ions constitutes an electrical current, which completes the chemical hop and triggers the impulse in the postsynaptic muscle cells. The impulse in turn signals a contraction of the muscle.

It has recently become possible to measure the electrical current associated with single acetylcholine receptor channels. The channels seem to switch rapidly between "open" and "closed" — there are no "half-open" or "nearly open" channels. Typically a channel remains open for about a millisecond, and during this time about 20,000 sodium ions flow into the cell from the outside fluid.

These receptor molecules and their channels constitute the research interest of my laboratory at Caltech. Ion channels are not restricted to the postsynaptic membrane of the nerve-muscle synapse. In fact, such channels occur in the membrane of every known nerve and muscle cell. Some ion channels allow only sodium to flow through; other types specifically allow potassium, chloride, or calcium ions. As for the signals that open and close them, receptors can be found that open channels in response to the specific binding of most neurotransmitter molecules. Some channels actually open and close in response to electric fields across the nerve cell membrane; these latter channels are responsible for the propagation of the nerve impulse within the nerve cell. We might summarize by saying, then, that the various ion channels seem to govern most electrical activity, and therefore most signaling, within the nervous system.

In the specific case of the channel associated with the acetylcholine receptor, we have a structure that is quite susceptible to drugs, and in the past few years studies on this channel have yielded a clearer picture of how some drugs act. Curare, for instance, is used by South American Indians on their poison darts. The curare molecule sits on the acetylcholine receptor and prevents one or both of the acetylcholine molecules from binding to it. As a result, the channel cannot open, no ions flow, and the impulse cannot be transmitted from the nerve to the muscle. The hunter's prey is paralyzed. The most toxic component from cobra venom has a similar action. Generally the cobra's prey dies of asphyxiation because the nerve message cannot reach its diaphragm muscles.

Local anesthetics such as Novocain (procaine) also act at




Several drugs act on the receptors of the postsynaptic cell — and they act in different ways. In the topmost figure on the left, two acetylcholine molecules bind to the receptors to open the channel for normal ion flow. Curare and cobra toxin molecules sit on the receptors, preventing the acetylcholine from binding, opening the channel, and transmitting the impulse. Local anesthetics allow the channel to open but plug it prematurely, while ethanol affects the springiness of the membrane, allowing the channel to stay open too long. The graph on the right indicates the flow of ions against time for each of the four cases.

acetylcholine receptor channels. A schematic view of events is that a local anesthetic acts like a cork. Acetylcholine can bind in the normal way, and the channel opens normally — and incidentally to the same extent as it might if only acetylcholine itself were present — but the local anesthetic now enters the channel and plugs it. As a result, ion flow — and the electrical message — is terminated prematurely. Local anesthetics block several types of ion channel in this fashion; the most important clinical blocking action is on the electrically excitable channels that propagate impulses within nerve cells. Pain impulses are thus prevented from reaching the brain, a fact that may be of some comfort to you the next time you find yourself in the dentist's chair.

Ethanol (alcohol) also influences the function of acetylcholine receptors. This drug seems to modify the springiness of the membrane that carries all of these receptors and channels. Once again, a channel might open normally and to the same extent as it would normally, but when ethanol is present, the modified membrane allows the channel to stay open substantially longer than usual. This drug certainly does not work primarily at the nerve-muscle synapse, but every nerve cell has ion channels, and a great many of them may be modified by alcohol. Some, like acetylcholine channels, remain open longer than usual; for others, the modified membrane forces the channel to close more rapidly than usual. At this point we cannot describe in detail how these actions on membrane channels lead to alcohol's profound behavioral effects or to addiction.

With the opening of receptor channels, the nerve impulse has almost completed its chemical hop from the nerve to the muscle. One final event is crucial. Acetylcholine molecules leave the receptors as the channels close again, and a very efficient enzyme, acetylcholinesterase, now destroys them. Enzyme molecules are located in large quantities exactly where they are required — in the space between the nerve and the muscle. As a result, the average acetylcholine molecule is destroyed within less than a millisecond after it leaves the receptor. Some insecticides and nerve gases work by blocking acetylcholinesterase. Such treatments allow acetylcholine molecules to hop from one receptor to another, forcing too many channels to open for too long. Too many postsynaptic impulses are initiated, and spasms result.

I have exploited the nerve-muscle synapse to discuss a few key concepts about synapses in general. First, transmitter molecules are liberated into the space between the two cells by electrical impulses; second, transmitter molecules then act upon the postsynaptic cell to generate further electricity; and third, transmitter molecules are then destroyed by an enzyme.

These events occur not only at the nerve-muscle synapse but at synapses in the brain as well. Nerve cells in the brain are, however, more complicated than the average muscle fiber. Each muscle fiber receives only one synapse, but some brain cells receive thousands. They fall into two major categories. One class of synapses *excites* impulses in the postsynaptic cell, as happens at the nerve-muscle

synapse. The second class *inhibits* the action of the first class.

Inhibitory and excitatory synapses have very similar structures, although the cognoscenti can distinguish them in the electron microscope. The receptors and channels differ, however. The inhibitory synapses make an electrical short circuit for the excitatory synapses, decreasing their effect, much the way a car's headlights dim when the starter is operating. Any nerve cell in the brain is constantly computing the difference between the excitatory synapses and the inhibitory synapses, and the result determines the frequency of its impulses. If inhibition is stronger than excitation, the cell sends a fairly low frequency of impulses to other cells. If, on the other hand, excitation predominates over inhibition, the cell fires impulses at a high frequency, and substantial amounts of transmitter are liberated at synapses where our test cell is the presynaptic partner.

Inhibition plays a key role in information-processing, and more than half the brain's synapses may be inhibitory. Two of the known inhibitory transmitters are the amino acids, glycine and $\gamma$- (or gamma) aminobutyric acid (GABA). Glycine is an especially potent inhibitory transmitter in the spinal cord. The convulsant drug strychnine apparently blocks glycine receptors, perhaps in a fashion similar to the blockade of acetylcholine receptors by curare or cobra toxin at the nerve-muscle synapse. The result is that some nerve cells receive too little inhibition, excitation predominates, and convulsions occur.

The most commonly prescribed drugs in our society, Valium and its close relative Librium, may affect GABA receptors. Recent studies suggest that these chemicals cause the inhibitory channels to remain open longer than normal, similarly perhaps to the action of ethanol at the nerve-muscle synapse. As a result, GABA, the inhibitory transmitter, is much more potent than normal. How does modifying membrane channels lead to decreasing anxiety? At the moment we can't say.

Some details are known about two transmitter systems in the brain and about drug effects on these systems. Deep within the brain, one group of nerve cells produces a pigment that makes them appear darker than the surrounding structures; thus this group is called the substantia nigra — the black substance. These cells, which also produce the transmitter dopamine, send their branches to many other areas of the brain. At one such region, concerned with modifying voluntary motions of the body, dopamine is an inhibitory transmitter. In some diseased states, substantia nigra cells begin to die. The result is too little inhibition by dopamine at synapses concerned with the control of voluntary motion, and this leads to the tremor that characterizes Parkinsonism.

The simplest therapeutic strategy for Parkinsonism would be to inject the missing dopamine directly into the bloodstream; but such a treatment is ineffective because dopamine itself does not travel from the blood to the brain. However, knowledge of transmitter metabolism has led to a successful therapy. Clinicians exploit the fact that nerve cells make dopamine from the chemical DOPA, which does pass from the blood to the brain. The strategy, then, is to make increased use of the surviving substantia nigra cells by administering an excess of DOPA. These cells then make more than their usual share of dopamine and package it into synaptic vesicles. The synaptic vesicles fuse with the presynaptic membrane and liberate their contents of dopamine into the space between the presynaptic and postsynaptic cells, thus restoring the normal balance between the inhibitory effects of dopamine and the excitatory effects of other transmitters.

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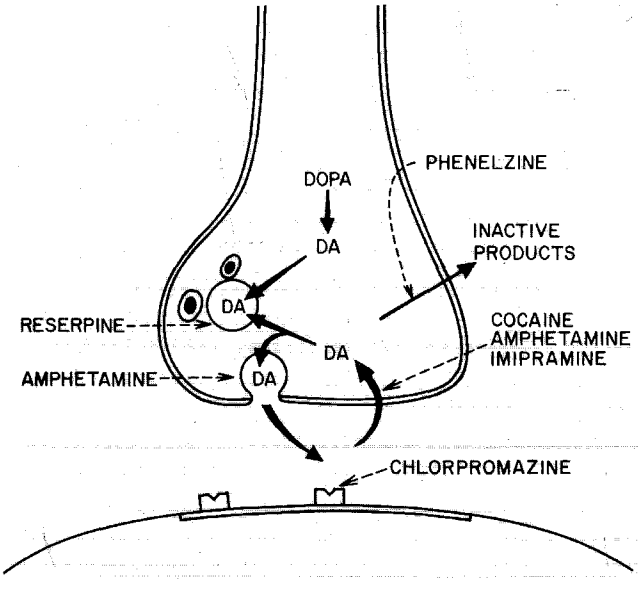


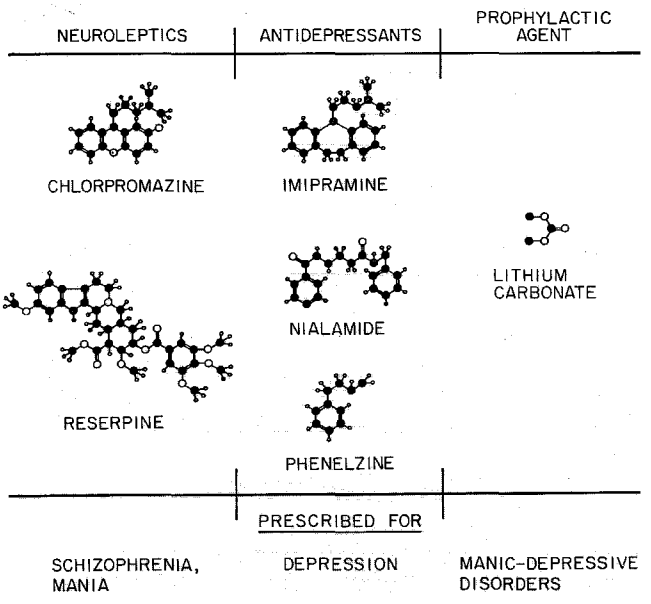

At different sites in the synapse various therapeutic drugs affect the action of dopamine, an inhibitory transmitter between nerve cells of the brain. Administration of DOPA allows increased production of dopamine (DA). Anti-depressant drugs imipramine (Tofranil or Elavil) and phenelzine also increase the amount of dopamine, phenelzine by blocking enzymes that inactivate it, and imipramine by interfering with the reuptake mechanism (as do cocaine and amphetamines). Reserpine and chlorpromazine work in the opposite way — to decrease the action of dopamine for treatment of schizophrenia. Reserpine prevents sufficient storage of dopamine in the synaptic vesicles, and chlorpromazine blocks the receptors.

The dopamine story has several other interesting chapters. In a small percentage of Parkinson's disease patients, DOPA therapy causes hallucinations and other symptoms of schizophrenia. These patients can be helped by other drugs, but such side effects remind us that substantia nigra cells release dopamine at synapses in many brain regions outside the one involved in Parkinsonism. Indeed, excess dopamine in some parts of the brain might cause forms of schizophrenia. This theory receives support from successful drug therapies that have been introduced over the last 25 years. For instance, chlorpromazine — the trade name is Thorazine — blocks dopamine receptors. As a result, even though too much dopamine might be released by a presynaptic cell at a synapse, if chlorpromazine is present the dopamine has less effect on receptors.

Apparently, chlorpromazine suppresses schizophrenic symptoms by restoring the normal balance between inhibition and excitation. Reserpine, from the snakeroot plant of India, was formerly in use for suppressing schizophrenic symptoms. This drug prevents efficient storage of dopamine in the synaptic vesicles of the presynaptic cell. Some of these synaptic vesicles are therefore empty when they fuse with the membrane. Less dopamine is released; the result, again, is a movement toward the normal balance between excitation and inhibition.

In some senses, schizophrenia can be contrasted with another class of mental disorders centering around depression. Some depressive states may arise because synapses have too little dopamine or the closely related neurotransmitter, noradrenaline (also called norepinephrine). Successful antidepressant drugs increase the level of these transmitters at synapses. Phenelzine, for instance (the trade name is Nardil), seems to block an enzyme that functions, like acetylcholinesterase at the nerve-muscle synapse, to inactivate the transmitter after it has bound to receptors. Thus phenelzine allows the remaining transmitter to have a greater effect, partially restoring the deficit.

Tofranil and Elavil, two other antidepressant drugs, enhance the effect of the remaining transmitter by interfering with another mechanism that normally terminates its action. The presynaptic cell can absorb the transmitter (dopamine or noradrenaline) into the cytoplasm. When this reuptake system is blocked, the transmitter again persists longer than usual. Interestingly enough, the reuptake system is also the site of action of the amphetamines and cocaine. These latter drugs produce a "rush" because they reach their targets within a few seconds — much more rapidly than the antidepressant drugs in clinical uses. Such differences provide a useful reminder that drug actions depend on a great many factors such as distribution, breakdown, and other effects in the body. For every drug that finds clinical use, a hundred may have been unsatisfactory because they acted too quickly, too slowly, or too broadly.




Of the above drugs, we know that five have large molecules and that they work by restoring normal levels of dopamine and norepinephrine action at brain synapses. Chlorpromazine blocks the receptors, and reserpine prevents sufficient storage of dopamine in the synaptic vesicles. The three in the center work in the opposite way — by blocking enzymes that inactivate or re-absorb dopamine and norepinephrine. The way lithium exerts its therapeutic effects is still unknown.

No one should infer that neurobiologists now understand completely the chemistry of mental disease and how to treat it. The use of the drug lithium is a case in point. This simple ion, which is quite effective against mania and manic-depressive disorders, strongly resembles sodium. It might, therefore, act at many different places in the nervous system, but we still have very little idea about the site where it produces its remarkable therapeutic effects.

One should also not infer that all transmitters act by opening channels in postsynaptic membranes. It is known that receptors for some hormones are coupled to enzyme molecules rather than to ion channels. The enzyme molecules produce a second transmitter molecule that acts *within* the receiving cell. This second transmitter is often cyclic AMP (adenosine monophosphate), which is made from the ubiquitous source of energy for physiological reactions, ATP (adenosine triphosphate). Cyclic AMP serves as an intracellular signal to activate second messengers in some parts of the nervous system. Like the transmitters themselves, the second messengers are usually de-

stroyed by an enzyme. This enzyme is highly sensitive to caffeine and theophylline, the drugs from coffee and tea. These beverages, then, prolong the action of intracellular transmitter molecules.

*Papaver somniferum,* the poppy that brings sleep, has been employed by man for thousands of years. Morphine, which is extracted from the opium poppy, is one of our most useful painkillers. Unfortunately, morphine is also addictive. Many factors make up addiction — some are sociological, some are psychological. Addiction is also observable at the level of cellular neurobiology. If a nerve cell is exposed repeatedly to morphine, the morphine loses its anesthetic effect. Increased doses become necessary because the cells become *tolerant* of the morphine. At the same time, the nerve cells change — in some fashion that is not understood — so that they cannot function normally without morphine; that is, they become *dependent* on morphine. These two interconnected phenomena, tolerance and dependence, underlie a large part of addiction.

Is there any hope for a nonaddictive painkiller that would not produce tolerance and dependence? To search intelligently for such a drug, we need to know more about morphine's action on the brain. Morphine is not present naturally in the brain, but morphine molecules do bind to cells of the so-called limbic system, a loosely connected ring of structures at the edge of the cerebral cortex. This system is importantly involved in perceiving pain. The straightforward hypothesis, then, is that these binding sites might also be sites of binding for a natural morphine-like substance produced by the brain. In other words, morphine might be mimicking a natural transmitter called into action to suppress pain during times of crisis or stress. Indeed, there is some evidence that such a transmitter is also released by acupuncture. Several research groups have therefore attempted to isolate and study the brain's own morphine-like substance.

The search, which began to show success about four years ago, exploited some similarities between nerve cells in the brain and those elsewhere in the nervous system. In addition to their action on the brain, morphine and its derivatives also suppress impulses in nerve cells of the digestive system, a fact appreciated by anyone who has cured the symptoms of an upset stomach by taking paregoric, which is an extract of opium. So the test for morphine activity involved soaking a bit of the intestine of a guinea pig in an organ bath. The tissue was stimulated with electrodes to produce impulses in the nerve cells that control the intestine's muscular activity. The strengths of the contractions were measured and provided a bio-assay for drugs that affect the nerve cells.

Morphine blocks the contractions, and a substance with similar effects was found in brain extracts. The substance is now called enkephalin, from the Greek meaning *from the brain*. Other pharmacological tests show that morphine and the enkephalins (there are a few, closely related molecules) act on the same receptors. Incidentally, the enkephalins are small proteins, unlike other transmitters I have described thus far. It is now becoming evident that many other transmitters in the brain are also small chains of amino acid residues.

Where are the cells that make the brain's own painkillers, the enkephalins? In large part they can be found in the limbic system, that region of the brain that suppresses our perception of pain. There is also enkephalin in the spinal cord, near the very first synapse that a pain impulse must pass to go from the outside world to the brain. At present we don't know where the enkephalins bind to their receptors or whether they open channels in postsynaptic cells. One possibility is that they inhibit the release of transmitter from the pain fibers at this first crucial synapse. This would prevent the pain signals from reaching the brain.

Thus far, the enkephalins do not constitute the sought-for nonaddictive painkillers, largely because, like most neurotransmitters, they are rapidly destroyed by enzymes that seem designed to terminate their action (as acetylcholinesterase inactivates acetylcholine). Therefore, direct injections of enkephalins have only a very weak action. Chemists have synthesized analogous molecules that are not subject to these enzymes. These relatives of the enkephalins do have painkilling action, but they also induce tolerance and dependence in the nerve cells — they are addictive. Despite these negative first results, there is good reason to expect further progress in this exciting new field.

An article on drugs and the brain would be incomplete without mentioning LSD, but we know embarrassingly few details about this drug. From molecular structures, we can say that LSD and psilocybin resemble serotonin, another known transmitter. It is possible to localize synapses where serotonin is the transmitter; and in animals given LSD these synapses become less active. So LSD and psilocybin might be blocking brain receptors for serotonin in the brain, but we have few clues as to how this might lead to hallucinations.

Neurobiologists seem to have made some progress since Freud asked, at the beginning of this century, whether psychiatrists and psychologists could put their science on a firm chemical basis. Freud would be pleased with the results so far, but he would certainly agree that the most exciting discoveries are yet to come. □