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The effect of psychochemicals on the higher central nervous system, and recent theories regarding drug addiction are discussed. The effect of drugs upon each individual is different. Many drugs have no effect on the brain because of a blood-brain barrier. However, alterations in the rate and character of one's metabolic pattern can lead to profound changes in brain function. Some psychochemicals exert their action by influencing the production and action of chemical transmitters, substances needed to stimulate or suppress brain activity. The chemistry involved in nerve cell activity and the effects of various drugs upon this activity are discussed as are the problems of drug synthesis and drug use by young people. (PS)

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The Biochemistry of Psychoactive Drugs [1]

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I am very pleased to be here and try to contribute to the accumulated ignorance in this field of knowledge. We know so little about how the central nervous system functions, but I am going to make an effort to describe how some of the psychochemicals may conceivably act on the higher central nervous system, and at least discuss some of the present-day theories regarding drug addiction.

As was pointed out earlier, the brain is simply a complex chemical system, perhaps the most complex in the universe; and in order to understand how chemicals will interact with such a complex chemical system we have to know something about what the brain is chemically and the peculiar chemical characteristics of psychochemicals which make them do what they do.

Drugs, especially the psychochemicals, do not produce the same effects in different individuals. Some individuals are stimulated by such drugs as barbiturates and morphine, while the majority of people are sedated. It is now known that there are genetic factors that help determine drug responsiveness. Other determinants include dosage, physical health, psychological constitution, environmental setting, and past and concurrent drug usage.

Lions, cats, and other felines respond to drugs in one way, and dogs and other canines will respond in an entirely different way. There are classical examples of this. Barbiturates, for example, will give a lion a bellyache. I am sure you have all heard the story about two lions who walked into a bar and ordered a drink. Shortly afterwards a luscious blonde entered and took a stool opposite them. One lion said to the other lion, "I think I will go over and eat that blonde," so he promptly went over, devoured the blonde, and came back. In a little while he began to develop a severe bellyache and said, "My, I feel awfully sick." The other lion said, "Well, it must have been that 'bar-bitch-u-rate'."

There are so many classes of psychochemicals that one can never hope in a day's time to cover the general field. In exploring the pharmacological literature one finds that all drugs, with few exceptions, affect some part of the nervous system. The reason why many drugs do not appear to have an

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action on the nervous system is because they cannot enter the nervous system from the blood stream. Between the blood and the brain there is a barrier called the blood-brain barrier, and this is the kind of restrictive filtering system that only allows certain types of molecules to enter the brain.

As a matter of fact, there are many substances normally present in the bloodstream to which the brain is extremely responsive and which, under normal conditions, cannot enter the brain. Potassium is an example. The brain is extremely sensitive to the potassium in the blood, which normally cannot enter. If, however, something happens to alter the blood-brain barrier, as during fever, certain infections, and severe trauma or shock, then the brain becomes responsive to potassium and other constituents of the blood.

The other thing we have to keep in mind is that the brain is sensitive to its own immediate chemical environment. During the normal course of metabolism there are hundreds of substances produced by the cells of the brain which are essential to brain function. Alterations in the rate and character of this "metabolic pattern" can lead to profound changes in brain function. An important group of such substances, which the present discussion will focus on, fall in the class of "chemical transmitters." It now appears that many of the psychochemicals exert their action by influencing the production and action of the chemical transmitters. Although there are many known chemical transmitters, there must exist so many more about which we know nothing.

Some chemical transmitters are needed to stimulate brain activity and others to suppress it. A drug which interferes with the action of the stimulating transmitter would, therefore, be expected to slow down brain function, while the opposite is true for a drug which affects the inhibitory transmitter. The question comes up as to why LSD produces hallucinations and amphetamine merely stimulates; or why morphine is a narcotic and analgesic while barbiturates produce sleep. There are many reasons why drugs possess such pharmacological specificity. One is because the peculiar chemical characteristics of the drug allow it to go to one part of the brain rather than to another. Another reason is that the drug affects systems in the brain which are localized in certain brain structures. With the evolutionary development of the central nervous system from lower to higher forms there was a concurrent biochemical or chemical evolution, so that specific kinds of chemical transmitters became associated with specific areas of the brain. By virtue of its chemical resemblance to a transmitter, a drug can be made to exert an action on those areas of the brain where the transmitter happens to be located.

Before proceeding we must say something about the function of the nervous system and how the chemical transmitters are involved in such function. In the laboratory the functional activity of the nervous system is examined by recording the electrical activity of the nerve cells. Such events as the transfer of messages, the storage of information, the coding of information, and all the various parameters used to describe the brain as though it were a computer are somehow tied up with this electrical activity. A great deal is known about how this electrical activity is produced and the physicochemical events underlying such activity.

In the nervous system there are some rather special membranes; these are responsible for generating the electrical activity by which we gauge nerve function. If one examines a section of the brain under the electron microscope,

he readily sees that the brain is made up largely of membranes in complex arrays. It is safe to say that the functional activity of the brain takes place primarily at membrane surfaces.

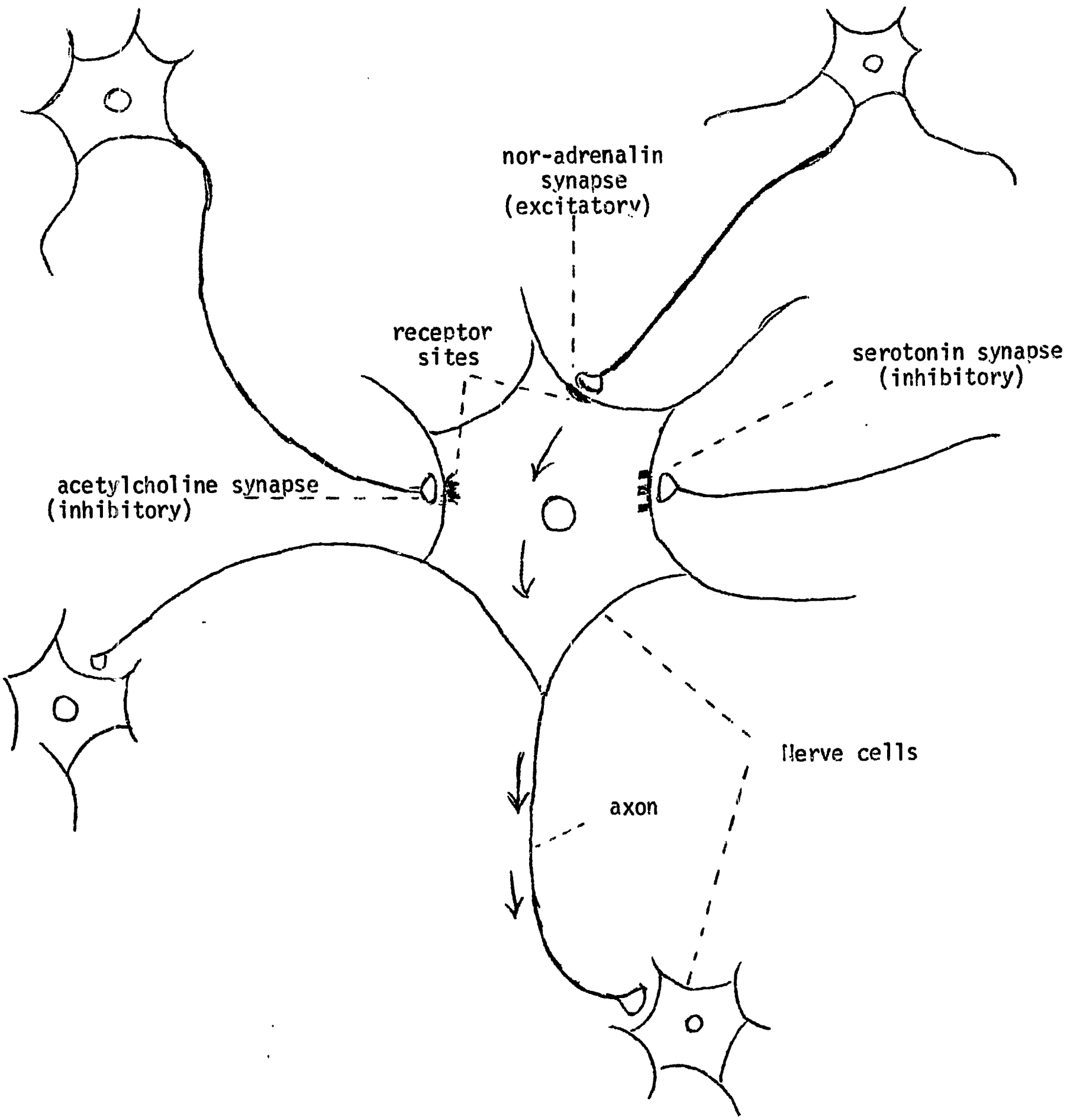
The way in which an electrical impulse is produced in a nerve cell is as follows: The cell membrane separates two solutions which differ greatly in their concentration of sodium ions. If something happens suddenly to change the membrane structure so that it cannot maintain this (thermodynamically) unstable concentration difference, the movement of sodium ions inward creates an electrical potential or impulse. The membrane is like a dam, and before a nerve impulse can occur it must open up to allow the electrically charged sodium to move inward. It is the movement of the ions which creates the electrical current that is recorded, just as the movement of electrons creates the electrical current. This is briefly how electrical activity is produced in the nervous system, except that millions of cells and membranes are interacting in complex patterns, the whole system becoming almost infinite in magnitude. It is said that the brain contains 10^9 cells and is capable of storing 10^{15} bits of information.

A major question confronting investigators in this field is the question of the membrane's chemical composition, and what it is that punctures the holes to allow ions to flow across. Something has to open the dam up, i.e., to produce holes in the membrane. We are beginning to understand something about this mechanism in the central nervous system, where most electrical transmission and excitation occurs at synapses. These are little connections on the surfaces of cells. One cell could have as many as 10,000 synapses, each coming from another cell, so one can readily visualize the complexity of the system, even in terms of a single cell.

In the chart on the following page I have indicated a scheme which might show how these synapses work and what the particular role of the chemical transmitter is. The big circle in the center is a nerve cell, and there are synapses at nine o'clock, one o'clock and three o'clock, ending at the cell surface. Within these synapses are tiny vesicles, little spheres containing chemical transmitters. As an electrical impulse enters the synapse from another cell, it causes the vesicles to break up and release chemical transmitters. Examples of such transmitters are acetylcholine, nor-adrenalin, and serotonin, all produced by the nerve cell within or very near to the synapse. By some obscure mechanism the transmitter is released and diffuses across the membrane of the synapse onto the cell surface where it then produces a nerve impulse by permitting the flow of sodium ions.

I have depicted three types of synapses on this particular cell, each of which is represented differently, suggesting that they are distinct and specific in some way. The region on the cell surface in contact with the synapse is called the receptor site. One of these receptor sites may be responsive to the chemical transmitter acetylcholine. Acetylcholine has to be released by the synapse before the cell will fire. The second receptor site can be assumed to be sensitive to another transmitter, nor-adrenalin, and the third to be sensitive to serotonin.

In what ways can drugs or other factors influence this system, assuming this to be a correct model for chemical transmission in this particular cell? Well, a drug could resemble acetylcholine chemically so that the receptor site is confused and cannot differentiate between acetylcholine and the drug.



CHEMICAL TRANSMITTERS IN NERVE EXCITATION

Nerve cells are linked together by means of connectors called "synapses." As an electrical impulse from a nerve cell reaches a synapse, it promotes the release of a chemical transmitter stored within the synapse. The transmitter diffuses to the receptor site and causes the second cell to discharge its own impulse. Some of the synapses release "excitatory" transmitters (e.g., nor-adrenalin), while others release inhibitory ones (e.g., acetylcholine and serotonin). If only an excitatory synapse is activated, the cell will "fire"; while the simultaneous activation of an inhibitory synapse will either prevent the cell from firing or modulate its response. A drug such as LSD occupies the receptor site at the serotonin synapse and, thereby, interferes with the action of the inhibitory synapse. The net result is an "overactivation" of the cell, since the suppressive or modulating influence is eliminated. (The arrows indicate the direction of the nerve impulse.)

Consequently, it latches onto the drug as readily as it does acetylcholine; however, the drug produces no response at the receptor site, because it does not fit properly. Since the receptor site is now occupied, acetylcholine in turn cannot exert its effect. An incorrect key is in the lock, and although the lock won't turn, the proper key cannot be inserted in the lock.

There are other ways in which drugs could interfere with the transmitter-receptor system. They could somehow affect the release of acetylcholine, or nor-adrenalin. As the nerve impulse releases the transmitter, a drug may somehow hamper the release mechanism. Morphine and related narcotics may be acting in this manner, i.e. they may prevent the release of acetylcholine.

On the other hand, a drug, instead of interfering, can accelerate the release of the transmitter. It can force the synapse to overexcite the cell by releasing more acetylcholine or nor-adrenalin. Examples of drugs which accelerate the release of nor-adrenalin are such stimulants as dexedrine and ephedrine. Still other drugs may act by preventing or accelerating the destruction of the chemical transmitter, thereby prolonging or shortening the duration of action of the transmitter.

An enzyme is usually involved in destroying the chemical transmitter once it has been released and exerted its action on the cell surface. If a drug interferes with the action of this enzyme and thereby prevents the transmitter from being destroyed, the cell continues to discharge nerve signals. There are many drugs which do this. A number of stimulating drugs used in treating depression act in this manner. They inhibit the enzyme which destroys the transmitter.

There is still another important way in which drugs can act on this system. Instead of confusing the receptor site, a drug may act on the site in very much the same manner as does the chemical transmitter, and actually excite the cell. There is, however,one thing wrong. There is an enzyme system or a mechanism for handling the normal chemical transmitter but not the drug which mimics the transmitter, so the system then begins to behave in an unorthodox fashion. I could go on and on describing other mechanisms and giving examples, but time does not permit this. Suffice it to say that most of the psychochemicals we know of act on one or more of these systems in a manner similar to what has been described.

I would now like to illustrate how some of the psychochemicals may act. LSD is believed to block the action of serotonin by occupying the serotonin receptor site. Consequently, serotonin cannot act, and this throws the serotonergic system out of whack. There are other hallucinogenic drugs, which are more powerful in many respects than LSD, which block the action of acetylcholine at the receptor site and which will prevent acetylcholine from acting. Acetylcholine in some parts of the brain may be an inhibitory transmitter, and by blocking its action the brain may be actually stimulated. Excessive stimulation may then result in hallucinations and other behavioral aberrations.

Chlorpromazine, a tranquilizing drug, blocks the action of nor-adrenalin at the receptor site. Since nor-adrenalin is an excitatory transmitter, a drug which interferes with its action would be expected to depress the

activity of the brain. Presumably, in the psychotic, disturbed patient there is an excessive output of nor-adrenalin or related stimulatory transmitters. These are some ways in which drugs can act on the central nervous system but by no means the only ways.

The action of a drug like morphine is diverse and extremely complex. Morphine is used in medicine to alleviate pain, i.e. as an analgesic. In some individuals it produces sedation and sleep, and in others stimulation and euphoria. Morphine evidently asserts its action in part by influencing those enzyme systems in cells which are responsible for the production of energy. In biological systems this energy takes the form of adenosinetriphosphate (ATP). By interfering with the production of ATP morphine prevents nerve cells from carrying out their normal function. Morphine is also known to actually substitute for certain enzyme systems and other essential chemical processes in cellular metabolism. This fact has led some people to speculate that morphine produces a physical addiction because of this biochemical dependence that results from continued usage. By the same token, sudden withdrawal of the morphine from an addict may be fatal because of the essential requirement of morphine for cellular function in the addict.

Barbiturates are equally diverse and complex in their action, and they too interfere with the production of ATP. Like morphine, barbiturates appear to interfere with certain enzymes involved in the utilization of oxygen by the cell, but barbiturates act on another important aspect of cell function and that is at the cell membrane.

I spoke earlier of the blood-brain barrier, the separation between the blood and the brain which is so essential for normal brain function. There are people today who believe that many drugs do not act directly upon the nerve cells in the brain but merely upon this blood-brain barrier, by altering its structure characteristics in such a way that certain psychoactive substances in the blood stream can now enter. For a while it was argued that even LSD acted in this fashion, and it is still possible that LSD probably acts in part by influencing the blood-brain barrier.

The brain is comprised of cells other than nerve cells and these are called glia. There are many types of glial cells whose function is largely one of supporting the nerve cell. Drugs will affect the metabolism of the glial cells, but although we don't know how this relates to brain function, the nerve cell cannot function properly without glia.

We are concerned today with rather specific psychochemicals. I looked over the list of drugs that was handed out to you, and it merely focuses attention on those drugs which are presently being abused and misused on college campuses. But the number of drugs which pose potential dangers and problems is much greater than what is contained in this list.

There are many narcotic drugs which are available to clinicians and investigators which are much more potent than morphine. To give you an example, there are narcotics which have recently been developed which are 10,000 times more potent than morphine, and it is believed that one exposure to a narcotic of this type will produce addiction. The other alarming thing is the fact that the chemical nature of these narcotics is, in many respects, more simple than morphine, so one with training in organic chemistry could go down in his basement and, perhaps, synthesize such substances.

One thing that has surprised me over the years is why more drug abusers have not taken to synthesizing their own drugs. Why bother about going to the pushers and others to get narcotics when many could be synthesized with a minimum of knowledge and assistance? With greater sophistication and technical training what is to prevent our young people in colleges from doing this? Indeed, attempts today are being made to synthesize LSD. If a person has the recipe for making it and has the starting products, he could come up with a product that might be 5-10% pure. Such a preparation may contain many dangerous impurities. There have been reports of students attempting to synthesize LSD. Much of the illicit LSD that is being distributed in this country and elsewhere is probably of this nature.

During and immediately after World War II, Japanese farmers were synthesizing amphetamines by the pounds in their own homes. Amphetamine addiction was a rampant problem in Japan at that time. Amphetamine (dexedrine) can be made by anyone with limited knowledge in organic synthesis.

This is the problem we are confronted with. What about all the drugs that young people do not presently have knowledge of or access to, which are so much simpler in their chemical nature that they can be readily synthesized. I am reluctant to mention this, but we know of simple substances which will produce psychoses lasting for days, which a sophomore in organic chemistry can synthesize.

As somebody pointed out, many of the students in colleges are brighter than we, and they would have no difficulty in making use of this knowledge if they were so disposed or if the circumstances were made available to them. I am merely pointing out that the present dangers in this area are extremely great, but the potentialities are even greater.

As knowledge of the relationship of chemical structure to pharmacological activity continues to improve, chemists will be able to develop more potent and unique psychotherapeutic drugs of immeasurable value to clinical medicine. The temptation to self-experiment with such novel psychochemicals will, I am certain, continue to increase.

Last but not least there is alcohol. Alcohol is the simplest of all drugs. It is the most readily available and among the most dangerous of all drugs. Yet, we do little to restrict its use and dissemination. There are drugs which will do what alcohol will do. In all likelihood we can expect more such drugs to be developed in the future. This should make our life both more interesting and considerably more complicated.

Our knowledge of how drugs act upon the nervous system is expanding at a phenomenal rate. Such knowledge not only leads us to the development of new and more powerful drugs, but aids greatly in our understanding of the nervous system. The psychochemicals have helped open up the brain to the experimentalists in a way probably not possible before.

This is the greatest use for the psychochemicals, and for this reason we must continue to have ready access to such substances in the laboratory. Since the problem of drug abuse helps curtail this effort, it is essential that we try to understand the problem and correct it as much as possible.