American Handbook of Psychiatry

Promising Directions in Psychopharmacology

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e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 6* edited by Silvano Arieti

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PROMISING DIRECTIONS IN PSYCHOPHARMACOLOGY

The discovery and testing of most drugs used in clinical psychiatry today occurred between 1940 and 1960. Although the introduction of new drugs has slowed considerably since then, significant progress has been made in understanding the mechanisms by which the "old" drugs exert their effects. This has, in turn, generated a number of useful hypotheses concerning the pathophysiology of mental illness which have been tested with varying success (see Chapters 21 and 23 in this volume) by direct measurement of brain function. As a result, hope has been generated that new drugs can be developed rationally from hypotheses about the biochemical alterations associated with certain psychiatric illnesses.

In this chapter, we will present an overview of some of the newer directions in psychopharmacology with particular emphasis on the development of "rational" drug-mediated interventions—rational in the sense that drugs are used to alter specific metabolic processes based on hypotheses of mental illness. This approach is relatively recent; previously, drugs have been developed by empirical or even serendipitous methods because knowledge of brain chemistry was simply too primitive to provide the basis for specifically planned interventions. This review focuses on current models of monoamine metabolism primarily because psychoactive drugs seem to have their most critical effects on neurotransmitter function.

The purpose of this chapter is to provide the practicing psychiatrist with an overview of developing trends in psychopharmacology by reviewing recent research in this field. Before presenting an outline for the rational development of new drugs, some of the more classical approaches will be reviewed.

Classical Psychopharmacology

Animal Screening

One strategy for the development of new drugs is the random screening of compounds for biological activity in animals. The main ingredients of the animal-screening method have been patience, persistence, and luck. For example, in 1952, Leo Sternbach, a chemist working at Hoffman-La Roche, formed some forty derivatives of a compound he had been interested in twenty years earlier. All proved to be pharmacologically inert. So, discouraged, he put the forty-first on the shelf. A year and a half later, during a cleanup of the laboratory, his assistant suggested that they send the shelved compound to the screening section for routine testing. It not only proved to be active, but was later found to be a most useful antianxiety agent. It was named chlordiazepoxide (Librium)

Currently animal screening for new psychoactive drugs is done for a

number of reasons. The most important is the necessary evaluation of drugs for toxicity, which can, in addition, produce information on probable pharmacological effects. For example, if animals die of intense sympathetic or parasympathetic stimulation, it is probable that the drugs will have autonomic effects at sub-lethal doses. Gross behavioral tests can sometimes give clues to the probable clinical effects of a drug; for example, spontaneous motor activity, ataxia, sedation, and blockade of tremors or convulsions induced by another drug such as metrazol or reversal of reserpine-induced hypothermia—all these effects are easily observed in animals and may relate to clinical efficacy in man.

Being able to predict psychopharmacological use in humans from animal-screening tests is difficult. Avoiding any preconceptions about the fundamental causes of anxiety, psychosis, or depression, experimenters have developed empirical-screening batteries of animal tests that can reliably discriminate among drugs that have an antianxiety, antipsychotic, or antidepressant effect. For example, the tests that best correlate with antipsychotic effects are shown in Table 24-1. It is still uncertain which of the effects shown in the table may be most specifically related to antipsychotic activity. For several years the inhibition of apomorphine-induced vomiting in dogs was the test most highly correlated with antipsychotic activity, simply because most known antipsychotic drugs were also antiemetic. The primary weakness of the empirical-screening methods is that they “find” drugs that

are similar to the ones we already have and quite possibly miss drugs with different pharmacologic properties that might be useful in the treatment of patients.

In recent years, efforts have been directed to the evaluation of new drugs, employing parameters in animal testing that may have more meaning for predicting psychological effects in man. Of importance has been the use of conditioning and learning techniques as formulated by the "behaviorist" psychologists. The behavioral paradigms are essentially derivatives of "classical" or "instrumental" conditioning. Utilizing these behavioral analyses, both antipsychotic and antianxiety agents have been shown to block avoidance conditioning. However, upon closer scrutiny, the avoidance behavior reduced by antipsychotic drugs is "active avoidance"; that is, the animal must actively make a response in order to avoid shock. In contrast, the antianxiety agents reduce "passive avoidance" in which animals are required to inhibit a usual response in order to avoid shock. Scheckel has suggested that the distinction between "active" and "passive" avoidance characterizes to some degree the effects of these drugs in man: for example, he has speculated that phobias (in which antianxiety agents are useful) can be thought of as examples of passive avoidance, and the schizophrenias (in which antipsychotic medication is helpful) can be thought of as instances of active avoidance, particularly of social and interpersonal experience. Such speculations are preliminary, but they demonstrate how refined techniques

of animal-behavioral analysis of conditioning and learning may produce some interesting theoretical insights into the mechanisms of action of pharmacological agents.

Table 24-1. Pharmacological Screening Tests for Phenothiazine-like Activity

Reduce exploratory behavior without undue sedation.
Induce a cataleptic state.
Induce palpebral ptosis reversible through handling.
Inhibit conditioned avoidance behavior.
Inhibit intracranial self-stimulation in reward areas.
Inhibit amphetamine- or apomorphine-induced stereotypic behavior.
Protect against epinephrine- or norepinephrine-induced mortality.

A promising direction, which may lead to more effective animal screening and which has more appeal to the dynamically oriented psychiatrist, is the production of psychiatric symptoms in animals, for example, depression produced in mother monkeys by isolating them from their young. Hopefully, this type of research will lead the way to "animal models" of psychiatric illness (see Chapter 15 in this volume) that can be used to test psychopharmacologic activity.

New Uses for Old Drugs

The gratuitous observation of psychotropic activity in a drug being used for other therapeutic purposes led to the discovery of both chlorpromazine and the MAO (monoamine oxide) inhibitors. In case of chlorpromazine, the path from synthesis to acceptance was most circuitous. Although synthesized

in 1944 by Paul Charpentier, chlorpromazine was initially rejected as having no therapeutic potential since it did not have very significant antihistaminic potency. Consequently, the clinical chapter of the chlorpromazine story began in 1949 when the surgeon Henri-Marie Laborit hypothesized that surgical shock was due to an overreaction of the autonomic nervous system. He began treating patients pre-operatively with promethazine, a potent antihistaminic with sympatholytic and parasympatholytic properties. He noticed, to his surprise, that the patients treated with promethazine were calm and appeared to suffer less, even after major operations, than patients not treated with promethazine. His interests then changed course, and he began to consider the possibility of developing a technique of surgery without anesthesia by using drugs that had a calming effect but did not put patients to sleep. This hope was only partially realized with the combination of antihistamines called the "lytic cocktail."

Laborit began searching for a drug with more powerful central effects. In 1951, chlorpromazine was given a clinical trial and was found to produce a "disinterest" in the treated patients. Laborit became quite enthusiastic about his newly found drug and spread the word to many other specialties. Psychiatrists were at first quite reluctant to try it: so many drugs had been tested unsuccessfully on their patients that they were quite skeptical. When, in 1952, Laborit finally did persuade some of his psychiatric colleagues to try the drug, the results were dramatic. In the course of a single year, the

treatment of psychosis was revolutionized in France and Italy. Acceptance in the United States came somewhat more slowly. Through numerous double-blind studies the effectiveness of chlorpromazine in the reduction of psychotic symptomatology was proven beyond reasonable doubt.

Another example of serendipity in the development of a psychotropic drug was the discovery of the MAO class of antidepressants. Selikoff and Robitzek reported that the anti-tubercular drug, iproniazid, had remarkable mood-elevating properties. The demonstration of this drug's main mechanism of action, that of monoamine oxidase inhibition, was made almost simultaneously. Subsequently, the drug was recognized as a useful antidepressant.

Isolation of Active Plant Extracts

The rauwolfia alkaloids were first isolated from plant extracts. Reserpine, an alkaloid, is one of the most potent antihypertensive agents known to man. Possibly the folk remedies of primitive societies have not been mined thoroughly enough for psychoactive drugs. Perhaps some interesting new compounds, useful in the treatment of mental illness, will be developed from current research on the cannabis plant. Snyder has noted euphorigenic effects of some tetrahydrocannabinol (THC) derivatives.

Modifying Existing Drugs

A more direct road to the development of psychopharmacologic agents has been the imitation of already existing, well-tested compounds. For example, the development of the thioxanthenes was accomplished after recognition that the aromatic nitrogen atom of the phenothiazines could be replaced by a carbon. Imipramine was synthesized by replacing the phenothiazine sulfur atom with a dimethyl bridge. For amitriptyline, the central nitrogen atom of imipramine was replaced with a carbon atom. Thus, relatively minor structural changes can produce important differences in pharmacological activity. This approach is vigorously pursued by competing drug firms in their attempts to circumvent competing patent laws.

Serendipity

The use of lithium salts for the treatment of mania was discovered by a remarkable series of observations. In 1949, John Cade, at the time an unknown psychiatric researcher working in a small hospital on limited funds in Western Australia, attempted to test the hypothesis that manic excitement was the result of intoxication from a normal body product analogous to thyrotoxicosis. His first step was the isolation of the toxic substance from the urine. After several experiments in which he injected urine from manic patients into guinea pigs, it was not too surprising that he found the most toxic substance in the urine to be urea. Cade became interested in the effect of urate salts on the toxicity of urea. Choosing the most soluble urate available,

the lithium salt, he found that it produced a protective effect on the convulsive mode of death produced by urea and, as luck would have it, the lithium ion, not the urate, was proven to be responsible for the effect. Furthermore, he noticed that animals injected with lithium salts became unusually placid. From these observations in animals, a trial of lithium in manic patients was initiated. As luck would again have it, the dose chosen was 600 mg. per day, close to the optimal range that has since been established. The only bad luck in this story was that during the year of the initial therapeutic success with lithium, a number of deaths were reported from lithium used in the treatment of congestive heart failure. Consequently, it required a large amount of research to validate the original observation sufficiently to allow the use of lithium in the treatment of mania.

Discoveries in psychopharmacology have been erratic and serendipitous. Little was known about the biochemistry of the brain when the afore-mentioned discoveries were made, so that a "rational basis" for the development of drugs was impossible. Although classical strategies continue to be practiced, many psychiatric researchers hope that an understanding of the pathophysiology of mental illness will bring even more significant discoveries than those made in relative darkness. However, this is a hope, and Jonathan Cole, one of the founders of the field of psychopharmacology offers this opinion on the development of antidepressants.

> Of all the approaches, I believe that I have the most intellectual enthusiasm for the rational basic science approach to the development of new and better antidepressants. However, if I had to bet money, I would bet that the next new wonderful antidepressant would be developed by serendipity out of some strange irrelevant area of medicine rather than by design out of a series of rational procedures. I hope I am wrong, [p. 86]

The Rational Approach

"Classical psychopharmacology" simplified the study of the effect of drugs on behavior largely by ignoring the intermediate levels. The input was drug, the output was behavior, and what was between was dimly known and for many purposes considered a "black box."

Since the development of the first few psychopharmacological agents, a large amount of information on the biochemistry of neuro-humoral synaptic transmission has become available. Furthermore, it has been discovered that most psychoactive agents have significant effects on some aspect of neurotransmitter metabolism. From the knowledge of the interactions of clinically useful drugs on the neurochemical events at the synapse, a number of hypotheses of the pathophysiology of mental illness have been developed. This approach to theorizing has been called the "pharmacological bridge." The "catecholamine hypothesis" of affective illness is the most coherent hypothesis of this type formulated thus far. This hypothesis states that depression may be associated with a relative deficiency of catecholamines at functionally important receptor sites in the brain and, conversely, that mania

may be associated with a relative excess. The catecholamine hypothesis of depression was largely derived from an analysis of the mechanisms of action of the effective drugs used in this illness. These compounds all seem to have the common characteristic of making catecholamines more available to the synaptic receptor, and thus intensifying or prolonging their effect. For example, the MAO inhibitors block degradation of monoamines and thus increase their concentration at the synapse. The tricyclic antidepressants block reuptake of monoamines, thus prolonging their effect at the synapse. Glassman has reviewed the evidence that serotonin, an indoleamine, may be deficient in depression. His rationale is similar to the arguments used to support the catecholamine hypothesis.

Theories of schizophrenia have been derived both from an analysis of psychotomimetic agents as well as of antipsychotic drugs. A number of endogenously formed psychotogenic amine derivatives have been suggested as important in the etiology of schizophrenia, but, as yet, no unifying coherent theory comparable to the catecholamine hypothesis of depression has been formulated. Recently, effects of therapeutic agents used in schizophrenia on the dopamine receptor sites in brain have been noted and this may result in the development of a pharmacological bridge.

Synaptic Physiology and the Development of New Drugs

The brain is made up of ten nerve cells that, although tightly packed together, are functionally quite isolated from each other, except for minute points along opposing membranes where information passes from one cell to another. These points, known as synapses, have been the focus of determined interest because they appear to be the anatomical locus of information transfer. Because synapses (in the periphery) and subsynaptic particles in the brain can be isolated for study, the knowledge of synaptic physiology has been greatly advanced since 1960.

In brief review, electrical impulses, the "markers" of neuronal information flow, are propagated along nerve cells in a stereotyped manner until they reach the area of the presynaptic membrane. Then, through a series of complex metabolic events, the electrical impulse is converted to a chemical message that effects the excitability of Neuron II by crossing the tiny gap between cells (see Figure 24-1). Depending on the type of neuro-regulatory agent mediating this transmission, and the type of receptor on the postsynaptic membrane, the chemical message can be excitatory or inhibitory. If more than one nerve cell impinges on Neuron II, the net excitability produced by the impinging synapses will determine whether or not Neuron II will depolarize and propagate an electrical impulse down its axon to another neuron.

The metabolic events of transmission are pictured in Figure 24-1.

The elucidation of the biochemical events underlying synaptic transmission has been one of the important achievements of the past two decades, culminating in a Nobel Prize in 1970 for one of the most important contributors, Julius Axelrod.

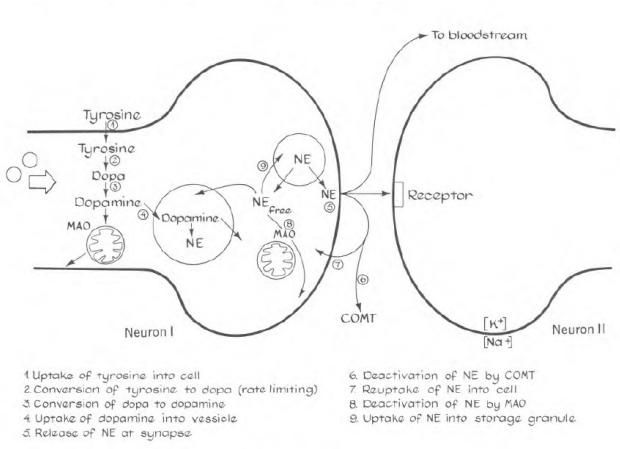

Figure 24-1.
The biochemistry of synaptic transmission. Adrenergic Transmission

Norepinephrine (NE) is synthesized in the region of the presynaptic membrane. It is made primarily from the amino acid tyrosine, which must be actively transported into the cell from the blood stream. The formation of Dopa from tyrosine by the enzyme tyrosine hydroxylase seems to be the slowest in the series of enzymatic reactions, so that this enzyme regulates, under ordinary circumstances, the amount of norepinephrine ultimately formed. Decarboxylation occurs in the cytoplasm of the cell by way of the

enzyme, L-amino acid decarboxylase. The product, dopamine (which may act as a transmitter itself) is taken up by the tiny vesicles and, therein hydroxylated, to form norepinephrine. Storage in the vesicle sequesters the synthesized norepinephrine and protects it from the intracellular enzyme, monoamine oxidase (MAO) that inactivates norepinephrine by deamination. As the electrical impulse activates the presynaptic membrane, norepinephrine is released into the synaptic cleft. Axelrod has hypothesized that the NE is squeezed into the cleft by contractile fibers in the vesicle membrane, a process that requires the presence of Ca++ and is accompanied by the release of dopamine beta hydroxylase. Once the norepinephrine has activated the receptor site on Neuron II, it is conserved by a process of reuptake back into Neuron I, although a portion is deactivated by an enzyme, located outside the cell and known as catechol-O-methyl transferase (COMT).

Table 24-2 reviews these processes and shows some of the actions of specific drugs on neurotransmission. Table 24-3 shows similar processes for the serotonergic synapses. Theoretically, for each metabolic step there is a possible pharmacological intervention.

Table 24-2. Synthesis and Metabolism of Norepinephrine

METABOLIC STEP	EFFECTED BY
1. Uptake of tyrosine into the cell.	1. Unknown.
2. Conversion of tyrosine to	2. (Tyrosine hydroxylase)Blocked by alpha methyl

Dopa.	tyrosine. May be effected by NE via negative feedback.
3. Conversion of dopa to dopamine.	3. (Dopa Decarboxylase)Rarely a critical step because of plentiful supply of decarboxylase enzyme.
4. Uptake of dopamine into storage vesicle.	4. Blocked by reserpine.
5. Conversion of dopamine to NE.	5. (Dopamine β-hydroxylase) Inhibited by disulfiram (chelating agent).
6. Release of NE into the synaptic cleft.	6. Stimulated by nerve impulses.
7. Deactivation of NE by COMT.	7. (Catechol-O-methyl-transferase) Inhibited by pyrogallol, N-butyl gallate.
8. Reuptake of NE into the cell.	8. Blocked by tricyclic antidepressants.
9. Intracellular deactivation of NE by MAO.	9. (Monoamine oxidase) Blocked by MAO inhibitors.
10. Uptake of NE into storage vesicle.	10. Blocked by reserpine.
11. Production of synaptic vesicles and transport down the axon.	11. Unknown.

Creveling and Daly have published an excellent review of the drugs that have been shown to have an effect on each of the steps in neurotransmission. As the steps of biogenic amine synthesis have been described, it has been possible to set up screening methods that test the effect of a particular drug on a specific process of neurotransmission.

Tyrosine Hydroxylase

Recently, a rapid, sensitive radiometric assay for tyrosine hydroxylase

has been developed, based on the stoichiometric loss of tritium during hydroxylation of 3,5-ditritiotyrosine. This assay may be conveniently employed as a screen for potential inhibitors of tyrosine hydroxylase. Such screening procedures do not have any direct relationship to the effect of the drug clinically, but, in combination with a theory about the disease process, a hypothesis about the therapeutic benefits of the drug may be formulated. For example, a drug that is a potent inhibitor of tyrosine hydroxylase would be expected to have a beneficial effect in mania, according to the catecholamine theory of affective disease, which relates mania to a functional excess of catecholamines.

As stated earlier, the hydroxylation of tyrosine is probably the rate-limiting step in catecholamine biosynthesis; consequently, any drug that affects the activity of this enzyme could be expected to have a prominent pharmacological effect on those moods or behavior related to neurotransmission involving catecholamines. A drug of this type which has received the most interest so far is a-methyl-p-tyrosine (AMPT). This drug is a potent inhibitor to the enzyme and is safe for clinical use. Studies by Brodie indicate that this drug may have some benefit in the treatment of mania.

Table 24-3. Synthesis and Metabolism of Serotonin

METABOLIC STEP	EFFECTED BY
1. Uptake of tryptophan into the cell from the	1. Plasma tryptophan concentration, diet, diurnal variation in tryptophan?

bloodstream.	
2. Conversion of tryptophan to 5HTP.	2. (Tryptophan hydroxylase) Blocked by parachlorophenylalanine. May be effected by serotonin via negative feedback.
3. Conversion of 5 HTP to 5 HT.	3. (L aromatic amino acid decarboxylase) Rarely a critical step.
4. Uptake of 5 HT into storage vesicle.	4. Blocked by reserpine.
5. Release of 5 HT.	5. Stimulated by nerve impulse.
6. Reuptake of 5 HT into the cell.	6. Blocked by tricyclic antidepressants.
7. Intracellular deactivation of 5 HT.	7. (Monoamine oxidase) Blocked by MAO inhibitors.
8. Production of synaptic vesicles.	8. Blocked by protein inhibitors.
9. Interaction with the receptor site.	9. Blocked by LSD? Blocked by methysergide?

It is likely that through the use of *in vitro* screening methods for drugs with tyrosine hydroxylase inhibiting activity other active compounds will be found that warrant a clinical trial in mania.

Jonsson has shown that the euphorigenic effects of amphetamine can be blocked by AMPT, thus providing evidence that the effects of amphetamine depend on intact catecholamine synthesis. It is possible that AMPT, or some other tyrosine hydroxylase inhibitor, may find use in the treatment of amphetamine abuse.

Tryptophan Hydroxylase

The pathway for serotonin biosynthesis has many parallels to the pathway for norepinephrine synthesis. The synthesis of norepinephrine involves the hydroxylation of an amino acid as the first enzymatic step; for serotonin biosynthesis, the first step is the hydroxylation of tryptophan to form 5-hydroxytryptophan. There is evidence that this hydroxylation step is rate limiting, and thus the ultimate concentration of serotonin may be regulated by the activity of this enzyme. However, tryptophan hydroxylase is not ordinarily saturated by substrate; therefore, increases in available tryptophan may readily produce increases in brain concentrations of serotonin.

The most effective inhibitor of tryptophan hydroxylase is p-chlorophenylalanine (PCPA). The specific action of this drug is unknown, but it is probably related to a long-term process such as protein synthesis. One of the most striking findings has been the production of insomnia in cats treated with PCPA. The use of this drug in psychiatry has been limited. Clinical trials in mania and perhaps schizophrenia are warranted since in both of these syndromes there is some rationale for decreasing the production of serotonin. Other inhibitors of tryptophan hydroxylase, such as the 6-halo-tryptophans and certain chelating agents, are available for animal studies. Interestingly, catechols, including norepinephrine, inhibit this enzyme. Such interactions

between the serotonergic and adrenergic systems seem to be the rule, making specific interventions in and on the other system difficult.

L-Aromatic-Amino Acid Decarboxylase

This enzyme is plentiful in the brain and elsewhere in the body. The same enzyme is active in the decarboxylation of Dopa to form dopamine and of 5-hydroxytryptophan (5-HTP) to form serotonin. The main clinical usefulness of decarboxylase inhibitors has been in association with the administration of large doses of precursors of biogenic amines. For example, in the treatment of depression with L-Dopa, the concomitant administration of a hydrazine-type decarboxylase inhibitor, which does not itself cross the blood-brain barrier, results in less peripheral decarboxylation of Dopa and in increased amounts of Dopa passing into the brain, for conversion to dopamine.

Dopamine Beta Hydroxylase (DBH)

This enzyme catalyzes the final step in the formation of NE from dopamine. Specific inhibitors of this step in norepinephrine formation may prove therapeutically useful.

Until recently, disulfiram (Antabuse) was the only inhibitor of DBH available for clinical use. However, recently a new nontoxic DBH inhibitor,

fusaric acid, has been discovered and reported to be useful in the treatment of hypertension. Both fusaric acid and disulfiram deserve clinical trials in mania on the basis that excessive concentrations of NE have been suggested as associated with the manic state.

Catechol-O-Methyl-Transferase

The metabolic inactivation of catecholamines proceeds by two major pathways: O-methylation produced by catechol-O-methyl transferase (COMT) and deamination carried out by monoamine oxidase (MAO). Various classes of compounds have been found to inhibit COMT. Perhaps the most potent are the pyrogallols. However these compounds are both quite toxic and short acting. The recent discovery of a nontoxic inhibitor of COMT available for use in man may prove of great importance in the study and treatment of psychoses.

Monoamine Oxidase

Evidence from a number of investigators indicates that MAO is not a single enzyme but a family of isozymes with differing substrate specificities. MAO is the enzyme responsible for intra-neuronal metabolism of catecholamines and serotonin, as well as other indoleamines such as tyramine and tryptamine. Since the discovery of the therapeutic value of the

MAO inhibitor iproniazid, a large number of compounds have been discovered that have MAO inhibiting activity. Much of the research in recent years on MAO inhibitors has focused on drugs that have fewer adverse side effects. This work has shown that the hydrazine-type MAO inhibitors are more often responsible for the liver damage and blood dyscrasias that occasionally occur with these drugs; consequently, efforts have been directed toward the discovery of non-hydrazine inhibitors. If safer and more effective MAO inhibitors can be found, use of these compounds in the treatment of depression may find renewed popularity. In addition, chemical testing of the spinal fluid from depressed patients may reveal which neurotransmitter is functionally deficient. The administration of a MAO inhibitor that blocks the isozyme specific for the deamination of that neurotransmitter may prove to be the treatment of choice.

Transport, Storage, and Release of Biogenic Amines

The processes of active membrane transport, intracellular storage, and release of amines upon stimulation, all affect the functional activity of amines. The tricyclic antidepressants are thought to be effective in depression because they inhibit reuptake of the amines into the nerve cell and thus prolong their action.

Cocaine, chlorpromazine, and imipramine are drugs that block the

uptake of norepinephrine in sympathetic nerve tissue. Although they have similar effects on sympathetic nerves, they have very different behavioral effects. Less is known about the uptake of serotonin, since there is no convenient peripheral system available for study as there is for norepinephrine. However, serotonin uptake in brain slices is similar in many respects to the uptake of norepinephrine. Some of the tricyclic drugs are more potent in their action on norepinephrine uptake, whereas others affect serotonin uptake to a greater extent. The future will bring more understanding of the differential effect of drugs on these two systems, and on other less well studied transmitter agents.

Ordinarily, the transmitter substance is released as the electrical impulse depolarizes the presynaptic membrane. Calcium ions are essential for this release; lithium and bromide ions antagonize the release. The toxic effects of bromides and the effectiveness of lithium in manic stress may be explained by these actions. Reserpine releases norepinephrine by inhibiting the granule storage mechanism within the nerve, thus making norepinephrine susceptible to deamination. Other releasing compounds, such as tyramine and guanethidine, cause release by direct displacement of norepinephrine; this type of release is more physiological since the release transmitter interacts with the receptor and is metabolized by COMT. One of the recently discovered releasing drugs, 6-hydroxydopamine, causes irreversible damage to the adrenergic nerve cell, thus producing a selective

neuronal lesion. Stein has suggested that a small amount of this compound, formed endogenously, could be responsible for the production of schizophrenia; this suggestion remains highly speculative. However, the selective ablation of adrenergic nerves with 6-hydroxydopamine will be an important research tool in the future.

In summary, the ease with which amines cross certain membranes in the CNS (central nervous system) is a most important factor in their biological activity. The effect of drugs on these membrane-mediated functions is an area of intense research; in the future we may well expect that new drugs that affect these activities will be important tools for the psychopharmacologist. It may be that uptake, storage, and release are more important targets for intervention than synthesis and metabolism.

Receptor Site

Less is known about events at the postsynaptic membrane than at the presynaptic membrane. The study of receptor-site physiology is growing rapidly. Of importance is the finding that cyclic AMP (adenosine monophosphate) may play a role as a "second messenger" in the effects mediated by biogenic amines. Activation of adenyl cyclase by biogenic amines may catalyze the formation of cyclic AMP, which may activate further enzymatic activity within the neuron. The enzyme phosphodiesterase, which

breaks down cyclic AMP, has been shown to be highly concentrated at the postsynaptic membrane. Beer has shown that there is a strong correlation between antianxiety effect and the inhibition of cyclic AMP phosphodiesterase. The use of drugs designed to affect adenyl cyclase or phosphodiesterase may be appropriate in the treatment of some mental illnesses.

There is some evidence that the propagation of the subsynaptic impulse may be the result of local release of cyclic AMP and that the neurotransmitters may act on the cyclic AMP system rather than on the subsynaptic membrane. Certain mild stimulants, e.g., caffeine and theophylline, inhibit phosphodiesterase, the enzyme that hydroxylyzes cyclic AMP. It is quite possible that in the future more potent stimulants (or antidepressants) will be developed as a result of understanding this system.

Prange and his associates have administered thyroid extract (T-3) concomitantly with tricyclic antidepressants. They have shown a significantly briefer onset of action if this combination is employed as compared to tricyclics alone. The exact mechanism for this interaction remains unknown. It may involve an effect of T-3 on the receptor enzyme adenylyl cyclase. If this finding is substantiated, it may remove one of the serious disadvantages to the use of this group of tricyclic antidepressants. Kastin has shown that the thyrotrophic releasing hormone (TRH) may also have antidepressant

properties.

Precursor Loading in Depression

The administration of the dopamine precursor L-Dopa has proven effective in the treatment of Parkinson's disease, an abnormality in which a deficiency of brain dopamine had been documented by autopsy studies. This has increased interest in this strategy as a possible means of treatment of various psychiatric illnesses. As Kety has stated, the strategy of precursor loading involves three steps: first, the formulation of a hypothesis relating the concentration of some substance in the brain with a particular mental state; second, producing evidence, ordinarily derived from animal research, to show that administration of the precursor does in fact increase the concentration of the presumed deficient substance in the brain; third, testing the hypothesis clinically by administering the precursor and making carefully controlled observations of the patient's behavioral state.

In order to utilize a precursor, it must be able to cross the blood-brain barrier (BBB) (most of the transmitter substances themselves are not able to cross the BBB) and must be converted to the deficient substance without loss via alternate pathways. Using these criteria, there are but a handful of precursors that are practicable for altering monoamine concentration in the brain. For the catechol system, L-Dopa has been the most often used. It has

the advantage of crossing the blood-brain barrier and of having a demonstrated pharmacological effect in Parkinson's syndrome. It has the disadvantage that most exogenously administered Dopa is converted to dopamine, leaving norepinephrine concentrations relatively unaffected. Efforts have been made to produce precursors of norepinephrine. For example, dihydroxyphenylserine was at one time thought to be an effective precursor since it is converted directly to norepinephrine. However, recent studies cast doubt on the ability of this metabolite to form NE intra-neuronally.

Clinical success with Dopa in the treatment of depression has been limited. There have been a few reported cases of Dopa sensitive depressions, but only a few. As mentioned above, this failure may be due to the fact that Dopa primarily increases dopamine concentrations and not norepinephrine.

The clinical trials to date of the serotonin precursors, tryptophan and 5-hydroxytrypto-phane have been well-reviewed by Carroll. In summary, tryptophan seems to have some effect when used in combination with MAO inhibitors, but not when employed by itself. Claims for 5-HTP have been varied and this drug may still have clinical usefulness, although the more recent studies have not been encouraging.

The major difficulties in using both Dopa and 5-HTP are related to the

finding that the drugs have peripheral effects so that dosages must be increased slowly. Furthermore, as additional knowledge becomes available about compartmentalization within the nerve cell, the more likely it becomes that monoamine concentrations may be increased by precursors without increasing the pool of amines that would be necessary to effect a change in physiological function. Furthermore, it is possible that the neurotransmitter synthesized from the administered precursor will be stored and released in neurons not normally utilizing this neurotransmitter, e.g., dopamine storage and release in a serotonergic neuron. If this were to occur, the newly synthesized biogenic amine would act as a false transmitter, decreasing neurotransmission. Lastly, there has been the problem of selecting patients for precursor loading; even though most of the patients studied to date failed to respond to precursor administration, there might be a subgroup of patients with a specific biochemical abnormality that could make them amenable to precursor therapy. More will be said about predicting drug response in a later portion of this chapter.

Future Directions in the Use of Lithium and Rubidium

Lithium was first demonstrated to be effective in the manic phase of manic-depressive illness. Although the prophylactic use of lithium had been suggested earlier, Baastrup and Schou were the first to report a systematic study that showed that lithium was effective in reducing the frequency and

intensity of both manic and depressive episodes when used prophylactically. Recently Coppen and Hullin have shown that lithium may be an effective prophylactic agent in both bipolar and recurrent unipolar depressions. It is possible that in the future the spectrum of use for prophylactic lithium will widen considerably and perhaps exceed in importance the role of the drug in the treatment of acute mania.

Recently, Fieve has reported preliminary pharmacological studies with rubidium. Rubidium belongs to the same series of alkali metals as lithium, sodium, and potassium. Interestingly, rubidium and lithium have contrasting behavioral, EEG, and biochemical properties. In contrast to lithium, which increases the uptake of norepinephrine into nerve cells, rubidium appears to augment the release of stored norepinephrine, thus increasing its turnover rate. Because preliminary studies in animals showed that the effects of rubidium were opposite to those of lithium, Fieve and his group have initiated clinical trials of rubidium in depressed patients. These experiments are proceeding cautiously since the toxicity of rubidium is unknown and since the metabolic half-life is long. Too few patients have been treated with the drug to allow clinical evaluations to be made as yet.

New Drugs for Mania

If manic illness is considered to be biochemically as well as behaviorally

the converse of depression, then drugs that decrease the amounts of amine available at the synaptic cleft should have therapeutic potential. Both antiadrenergic and anti-serotonergic drugs are currently being utilized in clinical trials. Administration of AMPT, a specific inhibitor of dopamine and norepinephrine synthesis, to manic patients has been reported to be of some benefit, as has propanolol a beta adrenergic blocker. Methysergide and cinanersin, both anti-serotonin agents have been claimed as effective for manic symptoms, but the results of trials to date remain controversial.

Approaches to Schizophrenia

Osmond and Smythies first formulated the "transmethylation hypothesis" of schizophrenia in 1952, when they made the observation that mescaline could be derived from norepinephrine by the addition of two methyl groups and suggested that a transmethylation enzyme could produce an endogenous psychotogen. The transmethylation hypothesis gained support when it was shown that other hallucinogens were methylated amines, for example, DMT (N, N-dimethyltryptamine) and bufotenin.' Kety and others showed that feeding patients compounds that would increase the supply of "methyl donors" in the brain could exacerbate the symptoms of schizophrenic patients.

The transmethylation hypothesis suggested a possible treatment

approach to schizophrenia, namely, the administration of a methyl "acceptor," nicotinic acid. Although positive reports continue to appear, the utility of nicotinic acid, either by itself or in combination with phenothiazines, is now considered minimal. Positive reports continue to appear. From a theoretical point of view, there is no direct evidence that nicotinic acid significantly affects the methylation capacity of the body.' Furthermore, this drug does not improve those patients who have been made worse by administration of methyl donors such as methionine. Since the transmethylation hypothesis remains a possible explanation for schizophrenia, a promising direction for future inquiry is the search for drugs that affect methylation processes more directly and efficiently.

Administration of Precursors in Schizophrenia

One of the older theories of schizophrenia, first suggested by Woolley and now being reconsidered by others, is that the concentration of brain serotonin might be abnormally low in schizophrenia. The recent evidence for this proposal comes from a number of places: (1) it is suggested that the sleep abnormalities characteristic of schizophrenics may be due to insufficient quantities of serotonin; (2) potent serotonin depleting drugs such as PCPA produce a syndrome in animals that is suggestive of schizophrenia. Wyatt has recently been conducting a clinical trial in which 5-HTP, the precursor or serotonin, is being given to schizophrenics. He reports improvement in

chronic schizophrenics given high doses (6 to 12 g.) of 5-HTP with a peripheral decarboxylase inhibitor over a long-time course.

Recent reviews by Kety and Matthysse and Snyder highlight the importance of the dopaminergic system in schizophrenia. They note that phenothiazines and the butyrophenones affect dopamine receptors, and they hypothesize that some nigro-striatal tracks may be the site of action for the antipsychotic activity of these compounds. In addition, Kety and Matthysse have noted that the amphetamine psychosis, presumed to represent an exaggerated activity of dopaminergic synapses in the brain, is clinically quite similar to certain schizophrenic states. Electrical stimulation of certain dopamine-containing nuclei of the limbic system, specifically the nucleus of the diagonal band, has resulted in altered mental states in which thought regresses from the secondary to the primary process, and in which thought images are converted to hallucinations.

If, indeed, schizophrenia is a disease of dopaminergic activity, agents that affect the activity of dopa decarboxylase or dopamine beta hydroxylase may be effective in the treatment of this disorder. Other agents that affect the dopaminergic receptor site should prove clinically useful.

Other Transmitter Systems in the Brain

The adrenergic and serotonergic systems have been the most

thoroughly studied, not entirely because of their suspected importance, but because of the easy and sensitive fluorometric procedures for determining the pathways and metabolism of these systems. There are undoubtedly other transmitter substances in the brain that may be of equal importance but are more difficult to measure. Until recently, physiochemical methods for detecting acetylcholine were so insensitive that bioassay methods are required, resulting in rather desultory progress in the understanding of this system. Undoubtedly, in the next few years there will be increased knowledge of the relationship of cholinergic systems to the action of psychopharmacological agents, perhaps in a pattern similar to the evolution of knowledge about drugs and norepinephrine. Some phenothiazine drugs are potently anticholinergic. Furthermore, other types of anticholinergic drugs have been shown to be psychotomimetic.

Janowsky has proposed that the adrenergic-cholinergic balance in the CNS may be an important factor in affective disease, depression being related to cholinergic dominance and mania the converse. As evidence, he cites the fact that reserpine, a drug that may trigger depression, has cholinomimetic properties as well as its better known NE releasing effects. In addition, he points out that physostigmine, which increases central acetylcholine levels in the brain, counteracts mania and may cause depression in some individuals. Other examples of adrenergic-cholinergic antagonism from animal studies are presented in his review, which supports the thesis that the relative balance

between the two systems may be of more importance than the level of activity of either system considered independently.

Some compounds with neurotransmitter-like activity are gamma aminobutyric acid, glycine, glutamic acid, and histamine. The effects of drugs on these neurotransmitter systems may be extremely important in the design of new and better psychopharmacologic agents.

Predicting Drug Response

One of the important tasks in psychopharmacology is the prediction of who will respond and who will not. Particularly in the case of the antidepressants there is a long latency between onset of treatment and response— usually from two to six weeks. Fawcett and Siomopoulos have reported the use of a trial treatment period with dextroamphetamine as a means of discriminating patients amenable to treatment with tricyclic antidepressants from non-responders. In their study of thirteen patients, they found a very good correlation between patients whose mood shifted upward during three days of amphetamine administration and eventual improvement subsequent to imipramine administration. This kind of screening procedure could prove valuable in allowing alternative drugs such as MAO inhibitors, or ECT, to be administered earlier in those cases where improvement on tricyclic medications, as judged by the amphetamine trial, would not be

predicted to occur.

With the recent development of sensitive methods of assaying psychotropic drugs in the plasma, it has been demonstrated that concentrations of tricyclic antidepressants in patients on a standard dose can vary considerably. Similar variability has been described for phenothiazines. Furthermore, a reduction in plasma antidepressant level was found in patients treated concomitantly with other drugs such as phenobarbital. Several investigators have reported that there is a positive correlation between plasma levels of tricyclic antidepressants and clinical response. Asberg found that most responders had levels in an optimal range between 50 and 139 nanograms per milliliter. Below that level, and interestingly, above that level, a clinical response was less likely to occur. It now appears promising that measurement of plasma levels of psychotropic drugs will be useful in predicting the treatment course of some patients who, because of some difference in metabolism or because of concomitant treatment with other drugs, require higher or lower doses.

Alexanderson has shown that individual differences in plasma concentrations of nortriptyline are largely under genetic control. In a study of nineteen identical and twenty fraternal sets of twins given nortriptyline for eight days, the identical twins achieved similar plasma concentrations of the drug while the fraternal twins had concentrations that were uncorrelated.

Thus, it appears that the science of "pharmacogenetics" may in the future advance our knowledge of differential response to psychotropic drugs, allowing more precise prediction of drug response.

A more distant goal for the psychopharmacologist is the use of laboratory methods to determine differences in patients that cannot be discriminated on purely clinical, psychometric, or pharmacological grounds. As a research tool, the measurement of biogenic amine metabolites in the CSF has been rewarding and in the future may lead to a more scientific choice treatment method.

An up-to-date review of the literature on amine metabolites measured in the CSF (cerebrospinal fluid) of patients with affective disorders has been provided by Post. In summary, discrepancies are prevalent. Some investigators have found a decreased level of 5-HIAA (5-hydroxyindoleacetic acid), the end product of serotonin metabolism, in depressed patients, but this finding is not confirmed by other studies. A similar state of confusion exists for HVA (homovanillic acid), the end product of dopamine metabolism, and for MHPG (3-methoxy-4-hydroxyphenylglycol), the primary end product of norepinephrine metabolism. Methodological difficulties may account for some of these inconsistencies; for example, Post has shown that physical activity can have profound effects on CSF amine metabolite levels.

A refinement in the measurement of CSF amine metabolites has been accomplished through the use of probenecid, administered prior to the collection of CSF samples. Probenecid blocks the transport of organic acids (including 5-HIAA and HVA) out of the CSF, resulting in an accumulation of these metabolites that is roughly proportional to the turnover of the parent amine compounds in the brain. Thus, it is possible, using probenecid, to obtain an indication of the dynamics of amine metabolism that is more relevant to the functional activity of these systems than is the measurement of the steady-state concentrations of amine metabolites. Using this technique, Goodwin has demonstrated significant alterations in CSF amine metabolites, not evident from "baseline" (no probenecid pretreatment) samples alone. In summary, the study of CSF metabolites is in a phase of methodological refinement. It has the potential of providing a clearer window into the brain than previous methods.

It is possible that as methods are improved and correlations more firmly established, categories of depression may become modified by our knowledge of pathophysiological changes as reflected in CSF metabolites. Such knowledge might improve the specificity of drugs. For example, there is evidence that the tricyclic antidepressants and MAO inhibitors differ with respect to their activity on adrenergic and serotonergic systems. If it could be shown that some depressed patients have a decrease of adrenergic metabolites in the CSF, they might be treated more effectively with drugs that

augment adrenergic activity. If some depressions are associated with deficiencies of serotonin metabolites, they might be best treated with drugs specifically designed to affect serotonergic systems.

Another approach that may provide useful laboratory correlations of psychiatric illness is the study of peripheral blood elements. Murphy has studied the amine metabolism of platelets from affectively disordered patients because of the similarities between the amine metabolism of platelets and the amine metabolism of brain. If one assumes that certain biochemical abnormalities associated with affective illness are systemic and not confined to particular areas of the brain, then the enzymes of the peripheral blood cells may reflect the important changes related to affective illness. Murphy has reported significant reductions in platelet MAO activity in drug-free bipolar patients (patients with a history of both mania and depression) as compared to unipolar patients and normal controls. Cohn has found red blood cell COMT to be reduced in depressed female patients. Unfortunately, in both these studies of blood-cell enzymes, the overlap between patient groups and controls has been large. However, the approach of studying the amine metabolism of the peripheral blood elements may in the future be a helpful adjunct to diagnosis and a guide to appropriate drug therapy.

Stokes reported a clinical test in which lithium “responders” could be

discriminated from “non-responders” on the basis of the rate of excretion of lithium after a standard dose. More recent reports on this simple biochemical test have been disappointing.

Delivery Systems

From the most primitive days of pharmacology, the modes of delivery of therapeutic compounds have not changed much. Oral, intramuscular, and intravenous administration continue to be the exclusive routes for getting drugs to target organs. The obvious drawbacks of oral administration are the unreliability of the patient, the variability of the absorption process, and differences in factors that affect blood concentrations. Furthermore, the concentrations of drugs orally administered are variable rather than static.

The discovery of long-acting, slow-release compounds has increased the physician s ability to decrease the frequency of drug administration. The use of depot injections of prolixin has added somewhat to the usefulness of phenothiazines by allowing physicians to medicate the unreliable patient at biweekly intervals rather than three to four times a day.

The blood-brain barrier, which has been the nemesis of many psychopharmacologists, may turn out to be a useful ally in the future. An example of the utilization of the blood-brain barrier for more discriminating drug delivery is the combined use of L-Dopa and a peripheral inhibitor of

Dopa decarboxylase (MK 486). L-Dopa has a number of peripheral side effects that limit the amount that can be administered and the rate at which dosage can be built up. MK 486 blocks the effects of L-Dopa, but since it does not cross the blood-brain barrier, it has no effects on the central action of the drug. Thus, by using these drugs in combination, the peripheral effects can be partially blocked and higher concentrations of the drug achieved in the brain. The utilization of the blood-brain barrier for discriminative delivery of drugs to the brain has probably not been used to full advantage.

Delivery systems have recently received increasing attention. One new pharmaceutical company is devoting itself exclusively to the development of improved delivery technology and has already developed some ingenious ways of administering drugs for certain nonpsychiatric illnesses. For example, a very small plastic membrane, which is worn comfortably in the conjunctival sac and releases miniscule amounts of pilocarpine at the rate of ten micrograms per hour, is now being used in the treatment of patients with glaucoma. Another system under development is a tiny capsule that is fitted in the uterus for the release of very small amounts of progesterone for the purposes of contraception. The great potential advantage of this system is that it bypasses the systemic circulation and thus avoids the many unpleasant side effects of oral birth control pills. In the future, delivery systems may be developed that can be modulated by an external source, such as a radio-transmitted message or an internal assessment of chemical concentrations

within the body. For example, it may be possible to devise a system that would release insulin in a rate proportional to the blood level of glucose. A more radical development, which is not inconceivable, is the stereotaxic placement of tiny seeds of slow-release medication in precise areas of brain.

Conclusion

Most of the psychopharmacologic agents in use today were shown to have a therapeutic effect in the treatment of mental illness by processes best explained as serendipitous and fortuitous. From these chancy, yet astute, observations have come compounds that have effectively decreased the number of inpatients in our state hospitals. Biochemical studies concerning the mode of action of these compounds have provided us with several hypotheses relating to the neurochemical substrates of schizophrenia and the major affective disorders. Most of these hypotheses originated in the mid-sixties. During the last few years, these hypotheses have provided the psychopharmacologist with a rationale for the design of compounds tailored to overcome the presumed biochemical defect in these illnesses. From further clinical trials with these compounds, as well as from new research on neuronal transmission, there should emerge a new science of psychopharmacology in which serendipity will be replaced by the rational construction of a therapeutic molecule.

Bibliography

Alexanderson, B., D. A. Price-Evans, and Sjoqvist. "Steady-State Plasma Levels of Nortriptyline in Twins: Influence of Genetic Factors in Drug Therapy," *Br. Med. J.,* 4 (1969), 764-768.

Ananth, J .V., T. A. Ban, H. E. Lehman et al. "Nicotinic Acid in the Prevention and Treatment of Artificially Induced Exacerbation of Psychopathology in Schizophrenics," *Can. Psychiatr. Assoc. J.,* 15 (1970), 15-20.

Asberg, M., B. Cronholm, F. Sjoqvist et al. "Relationship between Plasma Level and Therapeutic Effect of Nortriptyline," *Br. Med. J.,* 3 (1971), 331-334.

Axlerod, J., R. A. Mueller, and H. Thoenen. "New Aspects of Storage and Release Mechanisms of Catecholamines," *Bayer Symposium 1900* Vol 2, p. 212. Berlin: Springer, 1970.

Ayd, F. J., Jr. and B. Blackwell, eds. *Discoveries in Biological Psychiatry.* Philadelphia: Lippincott, 1970.

Baastrup, P. C. and M. Schou. "Lithium as a Prophylactic Agent. Its Effect Against Recurrent Depressions and Manic Depressive Psychosis," *Arch. Gen. Psychiatry,* 16 (1967), 162-172.

Baldessarini R. J. "Factors Influencing Tissue Levels of the Major Methyl Donor in Mammalian Tissue," in H. E. Himwich, S. Kety, and J. R. Smythies, eds, *Amines and Schizophrenia,* p. 199-208. New York: Pergamon, 1966.

Ban, T. "Nicotinic Acid and Psychiatry," *Can. Psychiatr. Assess. J.,* 16 (1971), 413-431.

Beer, B., M. Chasin, D. Clody et al. "Cyclic Adenosine Monophosphate Phosphodiesterase in Brain; Effect on Anxiety," *Science,* 176 (1972), 428-430.

Braithwaite, R. A., R. Goulding, G. Theano et al. "Plasma Concentration of Amitriptyline and Clinical Response," *Lancet,* 1 (1972), 1297-1300.

Brodie, H. K. H. and F. K. Goodwin. "A Peripheral Decarboxylase Inhibitor in Depression," *Sci. Prov.*

Sum. Form, 123rd Annu. Meet APA (1970), 64.

Brodie, H. K. H., D. L. Murphy, F. K. Goodwin et al. "Catecholamines and Mania: The Effect of Alpha-Methyl-Para-Tyrosine on Manic Behavior and Catecholamine Metabolism," *Clin. Pharmacol. Ther.,* 12 (1971), 218-224.

Brodie, H. K. H., R. Sack, and L. Siever. "Clinical Studies of L-5-hydroxytryptophan in Depression," in J. D. Barchas and Usdin, eds., *Serotonin and Behavior,* pp. 549-560. New York: Academic, 1973.

Bunney, W. E., Jr. and J. M. Davis. "Norepinephrine in Depressive Reactions," *Arch. Gen. Psychiatry,* 13 (1965), 483-494.

Burrows, G., B. Davies and B. Scoggins. "Plasma Concentrations of Nortriptyline and Clinical Response in Depressive Illness," *Lancet,* 2 (1972), 619-623.

Cade, J. F. J. "Lithium Salts in the Treatment of Psychotic Excitement," *Aust. Med. J.,* 1 (1949), 349-352.

Caldwell, A. E. "History of Psychopharmacology," in W. G. Clark and J. del Giudice, eds., *Principles of Psychopharmacology,* pp. 9-30. New York: Academic, 1970.

Carroll, B. J. "Monoamine Precursors in the Treatment of Depression," *Clin. Pharmacol. Ther.,* 12 (1971), 743-761.

Cohn, C. K., D. L. Dunner, and J. Axelrod. "Reduced Catechol-O-Methyltransferase Activity in Red Blood Cells of Women with Primary Affective Disorder," *Science,* 170 (1970), 1323-1324.

Cole, J. O. "The Future of Psychopharmacology," in R. Fieve, ed., *Depression in the 1970's: Modern Theory and Research,* pp. 81-86. Amsterdam: Excerp. Med., 1970.

Collins, G. G. S., M. Sandler, E. D. Williams et al. "Multiple Forms of Human Brain Mitochondrial Monoamine Oxidase," *Nature,* 225 (1970), 817-820.

Cooper, J. R., F. E. Bloom, and R. H. Roth. *The Biochemical Basis of Neuropharmacology*. New York:

Oxford University Press, 1970.

Coppen, A., R. Noguera, J. Bailey et al. "Prophylactic Lithium in Affective Disorders," *Lancet,* 2 (1971), 275-279.

Creveling, C. R. and J. W. Daly. "The Application of Biochemical Techniques in the Search for Drugs Affecting Biogenic Amines," in J. H. Biel and L. G. Abood, eds., *Biogenic Amines and Physiological Membranes in Drug Therapy,* pp. 355-412. New York: Dekker, 1971.

Curry, S., J. Davis, D. Janowsky et al. "Factors Affecting Chlorpromazine Plasma Levels in Psychiatric Patients," *Arch. Gen. Psychiatry,*22 (1970), 209-215.

Dement, W., V. Zarcone, J. Ferguson et al. "Some Parallel Findings in Schizophrenic Patients and Serotonin-Depleted Cats," in S. Sankar, ed., *Schizophrenia: Current Concepts and Research,* pp. 775- 811. Hicksville, N.Y.: P. J. D. Publ, 1969.

Ellerbrook, R. C. and M. B. Purdy. "Capacity of Stressed Humans under Mega Dosages of Nicotinic Acid to Synthesize Methylated Compounds," *Dis. Nerv. Syst.,* 31 (1970), igh-197'

Ericsson, A. D. "Potentiation of the L-Dopa Effect in Man by the Use of Catechol-O-Methyltransferase Inhibitors," *J. Neurol. Sci.,* 14 (1971), 193-197.

Fabing, H. D. "On Going Berserk: A Neuro chemical Inquiry," *Am. J. Psychiatry,* 113 (1956), 409-415.

Fawcett, J. and V. Siomopoulos. "Dextroamphetamine Response as a Possible Predictor of Improvement with Tricyclic Therapy in Depression," *Arch. Gen. Psychiatry,* 25 (1971), 247-255.

Fieve, R. R., H. Meltzer, D. L. Dunner et al. "Rubidium, Biochemical, Behavioral, and Metabolic Studies in Humans," *Am. J. Psychiatry,* 130 (1973), 55-61.

Florendo, N., R. Barnett, and P. Greengard. "Cyclic 3', 5'-Nucleotide Phosphodiesterase; Cytochemical Localization in the Cerebral Cortex," *Science,* 173 (1971), 745-747.

Glassman, A. "Indoleamines and Affective Disorders," *Psychosom. Med.,* 31 (1969), 107-114.

Goodwin, F. K., R. M. Post, D. L. Dunner et al. “Cerebrospinal Fluid Amine Metabolites in Affective Illness: The Probenecid Technique,” *Am. J. Psychiatry,* 130 (1973), 73-78.

Hollister, L. “Chemotherapy of Schizophrenia,” in B. T. Ho and W. M. Mclsaac, eds., *Brain Chemistry and Mental Disease,* pp. 303-317. New York: Plenum, 1971.

Hullin, R. P., R. McDonald, and M. N. Allsopp. “Prophylactic Lithium in Recurrent Affective Disorders,” *Lancet,* 1 (1972), 1044-1046.

Janowsky, D. S., M. K. El-Yousef, J. M. Davis et al. “A Cholinergic-Adrenergic Hypothesis of Mania and Depression,” *Lancet,* 1 (1972), 632-635.

Jonsson, L. E., L. M.’ Gunne, and E. Anggard. “Blockage of Intravenous Amphetamine Euphoria in Man,” *Clin. Pharmacol. Ther.,* 12 (1971), 889-896.

Karczmar, A. G. “Central Cholinergic Pathways and Their Behavioral Implications,” in W. G. Clark and J. del Giudice, eds., *Principles of Psychopharmacology,* pp. 57-86. New York: Academic, 1970.

Kasti, A. J., R. H. Ehrensing, D. S. Schakh et al. “Improvement in Mental Depression with Decreased Thyrotropin Response after Administration of Thyrotropin-Releasing Hormone,” *Lancet,* 2 (1972), 740-742.

Kety, S. S. “The Precursor-Load Strategy in Psychochemical Research,” in A. J. Mandell and M. Mandell, eds., *Psychochemical Research in Man.* pp. 127-134. New York: Academic, 1969.

Kety, S. S., and S. Matthysse. *Neurosciences Research Program Bulletin,* Vol. 10. Brookline: Neurosci. Res. Prog., 1972.

Moir, A. T. B., and D. Eccleston. “The Effects of Precursor Loading in the Cerebral Metabolism of 5-Hydroxyindoles,” *J. Neurochem.,* 15 (1968), 1093-1108.

Murphy, D. “Amine Precursors, Amines, and False Neurotransmitters in Depressed Patients,” *Am. J. Psychiatry,* 129 (1972), 141-148.

Murphy, D. L., and R. Weiss. "Reduced Monoamine Oxidase Activity in Blood Platelets from Bipolar Depressed Patients," *Am. J. Psychiatry,* 128 (1972), 1351-357.

Osmond, H., and A. Hoffer. "Massive Niacin Treatment in Schizophrenia: Review of a Nine-Year Study," *Lancet,* 1 (1962), 316-319.

Osmond, H., and J. Smythies. "Schizophrenia: A New Approach," *J. Ment. Sci.,* 98 (1952), 309-315.

Pletscher, A. "Amine Precursors in the Study of Affective Disorders," 7th Int. Congr., Collegium Int. *Neuropsychopharm*, Prague, 1970.

Pollin, W., P. V. Cardon, and S. S. Kety. "Effects of Amino Acid Feedings in Schizophrenic Patients Treated with Iproniazid," *Science,* 133 (1961), 104-105.

Post, R. M., J. Kotin, F. K. Goodwin et al. "Psychomotor Activity and Cerebrospinal Fluid Amine Metabolites in Affective Illness," *Am. J. Psychiatry,* 130 (1973), 67-72.

Prange, A. J., Jr., I. C. Wilson, A. M. Rabon et al. "Enhancement of Imipramine Antidepressant Activity by Thyroid Hormone," *Am. J. Psychiatry,* 126 (1969), 457-469.

Reid, W. D. "Turnover Rate of Brain 5-Hydroxy Tryptamine Increased by D-Amphetamine," *Brit. J. Pharmacol.,* 40 (1970), 483-487.

Scheckel, C. L. "Preclinical Psychopharmacology," in W. G. Clark and J. del Giudice, eds., *Principles of Psychopharmacology,* pp. 235-254. New York: Academic, 1970.

Schildkraut, J. J. "The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence," *Am. J. Psychiatry,* 122 (1965), 509-522.

Selikoff, I. J. and E. H. Robitzek. "Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid," *Dis. Chest,* 21 (1952), 385-438.

Shopsin, B. and S. Gershon. "Chemotherapy of Manic-Depressive Disorder," in B. T. Ho and W. M. Mclsaac, eds., *Brain Chemistry and Mental Disease,* pp. 319-377. New York: Plenum, 1971.

Snyder, S. H. “Amphetamine Psychosis: A ‘Model’ Schizophrenia Mediated by Catecholamines,” Am. *J. Psychiatry,* 130 (1973), 61-67.

Stein, L. and C. D. Wise. “Possible Etiology of Schizophrenia: Progressive Damage to the Noradrenergic Reward System by 6-Hydroxydopamine,” *Science,* 171 (1971), 1032-1036.

Stokes, J. W., J. Mendels, S. K. Secunda et al. “Lithium Excretion and Therapeutic Response,” *J. Nerv. Ment. Dis.,* 154 (1972), 43-48.

Sulser, F. and E. Sanders-Bush. “Effect of Drugs on Amines in the CNS,” Ami. *Rev. Pharmacol.,* 11 (1971), 209-230.

Szara, S. “Dimethyltryptamine: Its Metabolism in Man: The Relation of Its Psychotic Effect to the Serotonin Metabolism,” *Experientia,* 12 (1956), 441-442.

Terasawa, F. and M. Masakuni. “The Clinical Trial of a New Hypotensive Agent, ‘Fusaric Acid’ (5-Butylpicolinic Acid); The Preliminary Report,” *Jap. Circ. J.,* 35 (i97i), 339-357.

Woolley, D. W. *The Biochemical Bases of Psychoses or the Serotonin Hypothesis About Mental Illness*. New York: Wiley, 1962.

Wyatt, R. J., B. A. Termini, and J. Davis. “Biochemical and Sleep Studies of Schizophrenia: A Review of the Literature 1960-1970. Part II. Sleep Studies,” *Schizo. Bull.,* 4 (1971), 45-66.

Wyatt, R. J., T. Vaughan, M. Galanter et al. “Behavioral Changes of Chronic Schizophrenic Patients Given L-5-Hydroxytryptophan,” *Science,* 177 (1972), 1124-1126.

Zeller, E. A. and J. Barsky. *“In Vivo* Inhibition of Liver and Brain Monoamine Oxidase by i-Isonicotinyl-2-Isopropyl Hydrazine,” *Soc. Exp. Biol. Med.,* 81 (1952), 459-461.