Medical Treatment of Mental Illness

Pharmacotherapies revolutionize psychiatric care and present scientific and ethical challenges to society.

Philip A. Berger

Summary. Psychotherapeutic drugs have dramatically improved the prognosis for patients with severe mental illness. The drug treatments are not a panacea. The medications sometimes cause irreversible side effects, and they are not helpful for all patients. They allow large numbers of individuals to leave the hospital, but to return to communities that are often poorly prepared to provide continuing care. Despite their limitations, psychotherapeutic drugs relieve a great deal of human suffering. They also involve psychiatry in modern biological science. This has led to the continuing search for more effective medications based on the study of possible biochemical substrates of psychiatric disorders.

Effective pharmacological treatments for mental illness have existed only during the last quarter-century. This period has also witnessed a revolution in the care of patients with psychiatric disorders, and the number of patients in state and county mental hospitals has sharply declined. The introduction and evaluation of drug treatments required the development of more accurate methods of classification and of assessment of severity, and better criteria of improvement in mental patients. These more accurate methods could then be applied to nondrug treatments that were introduced in the optimistic period that followed the first successful drug trials. The resulting combination of drug therapy and psychological or socioenvironmental treatment is responsible for the vastly improved prognosis for patients with mental illness today (*1*).

Psychotherapeutic drugs have also helped wed some aspects of psychiatry with biological science, a source of significant therapeutic advances in the other medical specialities. Biological psychiatrists attempting to explain pharmacotherapies have also begun to investigate possible biochemical causes of mental illness.

The author is an assistant professor in the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California 94305, and director of the Stanford Psychiatric Clinical Research Center, Palo Alto Veterans Administration Hospital, Palo Alto, California 94304.

The use of drug treatments for mental illness is not all positive: problems have arisen for patients, physicians, and society. The drugs are not ideal. Not all patients are helped, and many are only partially improved. Like other useful medications, the pharmacological agents used in mental illness can cause severe adverse reactions; some of these side effects are irreversible. Certain classes of drugs for psychiatric patients are toxic when taken in an overdose and thus can be used in suicide attempts. The use of psychotherapeutic drugs poses ethical questions for physicians and society. The symptoms of some mental disorders make it difficult for patients to understand their pharmacological treatments, and therefore they cannot base their decision on whether to take medications on a true understanding of the potential benefits and risks. Whether involuntary treatment of psychiatric patients is ever justified is the appropriate subject of vigorous debate. The factors that must be weighed include the patients' rights, the duties and responsibilities that a physician feels towards the patients, and the right of society to be protected from dangerous behaviors (*1*).

In this article I will discuss some of the practical, scientific, and ethical aspects of the medical treatment of mental illness. A description of the predrug era is followed by a discussion of the impact of recent therapeutic innovations. Three major psychiatric disorders are described: schizophrenia, depression, and mania. The important current drug treatments for these disorders are the antipsychotics for schizophrenia, tricyclic antidepressants or monoamine oxidase inhibitors for depression, and lithium salts for mania. Evidence for their efficacy, practical aspects of treatment, and critical evaluations of their hypothesized biochemical mechanisms of action are described. Finally, the ethical problems created by the drug treatments of mental disorders are outlined.

The Revolution in Psychiatric Care

Firsthand descriptions by physicians who worked with the mentally ill before the introduction of effective pharmacotherapies paint a dismal picture of the predrug era. There were few outpatient psychiatric clinics, and general medical hospitals rarely admitted patients with severe mental illness. Most patients were sent quickly to state mental hospitals, which were more like custodial facilities than medical treatment centers. Pessimism about psychiatric disorders was widespread, admissions increased, and discharges remained low.

Living areas in public mental hospitals were poorly furnished and crowded. Hallucinating patients paced the floor, or rocked in chairs, and talked to their "voices"; paranoid patients scanned the rooms, ever vigilant and ever fearful. Catatonic patients remained in fixed positions for days at a time, developing swollen limbs and pressure sores; withdrawn patients sat on wooden benches, year after year, doing nothing, while their physical health deteriorated. Manic patients joked, laughed, and moved about rapidly for days at a time until they collapsed, exhausted. Violent or agitated patients attacked other patients or staff members in response to idiosyncratic beliefs. Such patients were often kept in nearly empty "seclusion rooms," strapped to beds that were bolted to the floor or placed in warm baths or wrapped in wet sheets in an attempt to calm them (*1*, *2*).

The physicians responsible for the treatment of patients in public mental hospitals were poorly equipped for the task. Before World War II, many of these physicians were trained in general medicine or neurology; during the postwar period some had also studied psychoanalytic psychotherapy. However, neither neurological diagnosis nor psychoanalysis had much to offer patients in

0036-8075/78/0526-0974$01.50/0

public mental institutions. Thus, physicians acted mainly as custodians and administrators. Many of the people who worked in public mental hospitals were courageous and caring, but they faced an impossible task, not only because of the social stigma of mental illness, public apathy, and lack of adequate funds for patient facilities and staff, but also because there simply were few effective treatments for severe psychiatric disease (*1, 2*).

A dramatic change in the treatment of patients with mental illness began in the 1950's. For nearly 100 years, the number of patients in public mental institutions in the United States had increased by about 2 percent per year, reaching a peak of 559,000 in 1955 (Fig. 1) (*3*). Then in 1956, for the first time in history, more of these patients were discharged than admitted, a trend that continues despite a steady increase in both the admission rate and the national population. Today there are less than 200,000 patients in these institutions (*3, 4*). However, not even the majority of the individuals who leave public mental hospitals are free of psychiatric symptoms, and many continue to receive treatment in transitional facilities or outpatient clinics. Still, most are able to reestablish family relationships, find employment, and participate in community life (*1, 4*).

Conditions have also improved for patients in the hospitals. Very few patients require seclusion rooms and physical restraints; those who do usually respond rapidly to treatment. Most hospital wards are unlocked. Many are set up as "therapeutic communities," where patients and staff meet regularly to discuss all aspects of life in the hospital. Patients are treated with respect and encouraged to determine many of the conditions of their hospitalization. Increased patient government improves the hospital environment and also helps patients in the transition from hospitalization to home by making the hospital more like a family or a community. Other improvements in modern mental hospitals increase the similarities between the hospital and the rest of society. Plays, concerts, movies, sports equipment, and arts and crafts are available to most patients. Some psychiatric hospitals have small companies that contract to do piecework for local industries, so that patients can be economically productive even during their hospital stay (*1*).

These dramatic changes in the treatment of psychiatric patients are the result of many interrelated factors. Much of the momentum, however, came from

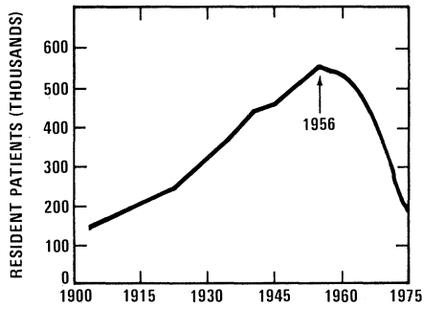

Fig. 1. Patient population in public mental institutions, 1900 through 1975 (*3*).

the development and use of psychotherapeutic drugs. Use of these drugs led to a climate that favored innovation and encouraged the development and evaluation of other new therapeutic approaches. As with all important social changes, there have been some negative results from the discharge of large numbers of patients from public mental hospitals. In some areas, planning was inadequate for the return of psychiatric patients to the community (*4, 5*). Reich (*6*) reports that many patients discharged from New York State mental hospitals are living in cheap hotels, where they are robbed and abused by people who take advantage of their relative helplessness. Arnhoff (*7*) suggests that the impact of community treatment on the families of mental patients has not been carefully studied. He finds no convincing evidence that home or community treatment is better than hospital treatment in either its short- or its long-term effects (*7*).

The location of psychiatric treatment is certainly less important than its quality. While much remains to be done, it is clear that the quality of treatment for patients with severe mental illness has vastly improved since the introduction of psychotherapeutic drugs.

Schizophrenia

The schizophrenic syndrome usually begins in young adulthood. Symptoms include altered motor behavior, perceptual distortions, disturbed thinking, altered mood, and unusual interpersonal behavior. Occasionally, a schizophrenic syndrome appears suddenly; more commonly the symptoms have an insidious onset. In many cases the patient has a history of being somewhat withdrawn and introverted since childhood. In the prodromal phase of schizophrenia, commonplace reality may begin to seem strange. Patients often withdraw into themselves to focus on internal experiences. Commonly they feel depersonalized, as if their identity were being dissolved or lost. Those close to these individuals often have increasing difficulty empathizing with and understanding their unusual feelings, thoughts, and experiences. Normal diurnal rhythms of sleep, appetite, and sexual interest may be disrupted. Gradually, full-blown schizophrenic syndromes develop. Although symptoms vary from patient to patient, they usually make normal functioning difficult or impossible.

The motor behavior of schizophrenics ranges from total immobilization, called catatonia, to frenetic and purposeless activity often accompanied by peculiar mannerisms. Perceptual distortions include hallucinations, which can arise in any sensory modality, although auditory hallucinations ("hearing voices") are the most common. Frequently, the voices are threatening or obscene and may instruct the patient to perform specific acts. Sometimes patients hear their own thoughts out loud. Disturbances in thinking in schizophrenic patients lead to distorted concept formation, bizarre speech, and illogical thought patterns. The illogical thought patterns are often expressed as delusions, ideas that are false or improbable but that cannot be modified by persuasion or contradictory evidence. Common paranoid delusions lead schizophrenic patients to believe that they have been chosen for special missions or that they are the object of persecution by a group with complex plots against them. Some schizophrenics have the delusions that unseen forces are controlling their thoughts or behavior or "reading their minds." Delusions are reinforced by misinterpretations of reality. Thus schizophrenics often believe that items on television or in newspapers are cryptic messages confirming their beliefs.

Schizophrenic patients also have disorders of the thought process. This causes the speech pattern to wander and fail to lead to its apparent goal, a process called looseness of associations. Expressions of emotion in schizophrenic patients are often absent, blunted, or inappropriate to the content of the conversation. Sometimes schizophrenics are overwhelmed with intense anxiety or deep rage, unrelated to any obvious environmental stimuli.

In schizophrenic patients these profound disturbances in motor behavior, perceptions, thinking, and mood cause severe difficulties in everyday tasks and interpersonal relationships. Patients often behave in an impulsive, dis-

organized, or unusual manner. Schizophrenic patients are rarely dangerous, but they are unpredictable and may occasionally act violently if directed by "a voice," if they feel they must defend themselves against an imaginary enemy, or if they are overactive and severely disorganized (*1, 8*).

What is the incidence of schizophrenia? At present about 180,000 patients are hospitalized in the United States with the diagnosis of schizophrenia; another 800,000 are being treated as outpatients or have active symptoms but are not being treated. The number of individuals who develop schizophrenic symptoms each year is approximately 150 per 100,000. The chances that a person will be treated for schizophrenia in his lifetime have been estimated to be about 1 percent. About half of the available beds for the mentally ill and the mentally retarded, or about one-quarter of all available beds in hospitals, are occupied by patients with the diagnosis of schizophrenia. Despite the widely held belief that schizophrenia is more common in complex modern societies, the incidence of schizophrenia has been relatively constant for the last 100 years in the United States. In addition, preliminary results of recent international collaborative studies show a similar incidence in all nations that have been studied (*9*).

Depression

The term depression is used to describe both a normal mood and a serious mental disorder. As a normal mood, depression refers to the transitory feelings of sadness, grief, disappointment, loneliness, or discouragement that everyone feels during the difficult times of life. As a mental disorder, depression is an illness with many symptoms, only one of which is sadness. Those with depression have changes in mood, thinking patterns, motor activity, and behavior. They also have somatic or physical symptoms and frequently have suicidal ideas that can lead to self-destructive behavior.

The mood of depressed individuals is variable but includes profound sadness and often a loss of the ability to feel pleasure. The ideas, activities, and relationships that usually bring pleasure can seem empty or hollow. The changes in thinking patterns lead to pessimism about the future and low self-esteem. Depressed people often deny their past accomplishments or feel unworthy of current achievements. Feelings of low self-esteem or worthlessness combine with pessimism to rob them of their motivation, making it difficult to maintain either jobs or interpersonal relationships. Often they feel guilty about not living up to the expectations of others. Guilt can be even more generalized, so that some depressed people may feel they have committed a sin or a crime and fear discovery or think they deserve punishment. Some severely depressed patients develop psychosis. A psychotic patient distorts or perceives reality incorrectly. This can lead to unusual beliefs or behaviors. For example, some depressed patients may feel they have actually become hollow inside, that their internal organs have "turned to dust." To give another example, a psychotically depressed individual may blame himself for a tragic world event such as a war or a flood. Many depressed people are fearful or anxious. They may be agitated and quite physically active but unable to concentrate on any task; or they may move very slowly, feel extremely weak, tired, and helpless, and have slow and labored thoughts that make it difficult to concentrate, to read, or even to form sentences for conversation.

Physical symptoms are often a prominent part of the depression syndrome. Those with severe depression often have no appetite and lose weight. Sleep disturbance is another common symptom, causing insomnia, restless nights, and early morning awakening. In severe depression a patient often wakes at 3 or 4 a.m. and is unable to get back to sleep. Some depressed patients also experience constipation, dry mouth, tight feelings in the chest, and aches and pains, particularly headaches and backaches. Many depressed people lose interest in sexual activity, and depressed women often have changes in their menstrual cycle.

Thoughts of death and suicide are the most dangerous symptom of severe depression. The hopelessness, guilt feelings, and low self-esteem can all contribute to suicidal thinking. Some patients see suicide as an escape from their psychic pain. Others feel there is no reason to go on living since things will never get better. Some believe that their death would relieve their family of the burden of caring for them; others feel that death is the appropriate punishment for their imagined sin or crime. Whatever the cognitive origin, suicide must be considered a possibility in anyone with depression.

Most depressed patients do not have a history of any other psychiatric illness. About one-fifth of depressed patients have episodes of both depression and mania and are called bipolar patients. Unipolar patients are those who suffer only recurrent depressive episodes. This distinction between bipolar and unipolar depression is increasingly important in both research and pharmacotherapy (*9*).

Mania

Mania is a severe emotional disorder that superficially appears to be the opposite of depression. Symptoms can be divided into changes in mood, thought, motor activity, and behavior. The mood is elated—sometimes euphoric, overconfident, or carefree. A manic individual is optimistic and may feel attractive, desirable, efficient, and alert. However, this mood often is brittle, and these individuals become irritable if frustrated. The thought patterns of manics are disturbed, with one thought rapidly following another in what is called flight of ideas. Ideas of potency, knowledge, and special abilities occur in severe mania. The motor activity of manics is also accelerated; they are restless and may work energetically, but may move from project to project, unable to complete any. Manic individuals may sleep little and eat less; like patients with severe depression, they tend to lose weight. Mild forms of mania, called hypomania, may serve a person well, since our society is more appreciative of, and even selects for success, people with some manic traits in preference to more depressive or contemplative individuals. In contrast, severe mania causes significant life disruptions and can be devastating to personal relationships and careers.

Some bipolar patients alternate between depression and mania. However, many have long periods of normal functioning in between episodes. In general, manic episodes are more common when bipolar patients are younger, while depression is more frequent with age. The duration of the episodes of bipolar illness varies. One common pattern is for depressive episodes to last about 6 months and manic episodes about 3 months. However, a few patients have been known to cycle from mania to depression in periods as short as 24 hours, while others have manic and depressed episodes that seem to last for years (*10*).

How common are depression and mania? The major problem in determining the incidence is the lack of a universal definition of depression or mania. The incidence of bipolar illness is about 300 per 100,000 or 0.3 percent. Perhaps 600,000 bipolar patients are identified and treated each year in the United

States. The number of patients with severe unipolar depression is certainly much larger. According to the National Institute of Mental Health (NIMH) and other sources, some 1.5 million people are being treated for depression today. But perhaps three or even five times that number may actually need such treatment. Thus, there may be from 4.5 to 7.5 million individuals in the United States who are suffering the psychic pain, life disruptions, and risk of suicide associated with depression and who could benefit from treatment. The results from an NIMH and a British study suggest that perhaps as many as 15 percent of the population will have at least one depressive episode during their lifetime. There are at least 26,000 reported deaths by suicide each year, making it the tenth leading cause of death. Thus, depression and suicide are major public health concerns that require vigorous medical treatment (*10, 11*).

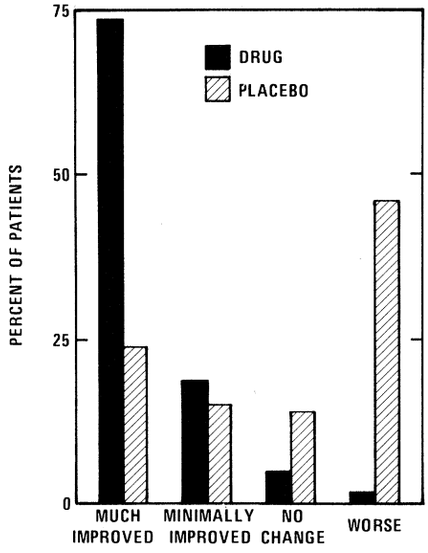

Fig. 2. Physicians' global ratings of patients' responses to treatment with antipsychotics or placebo (*13*).

Antipsychotic Medications

The drug treatments of schizophrenia include substances from at least eight different chemical classes. The drugs are remarkable in their ability to counteract hallucinations, delusional thinking, assaultiveness, severe excitement or withdrawal, and unusual behavior and to facilitate the social adjustment of schizophrenic patients. Unfortunately, they are not effective in all patients and are only partially effective in others. They can also have troublesome and sometimes irreversible side effects (*12*).

Several important questions can be asked about the antipsychotics: Are they effective when compared to a placebo? Are they useful as maintenance treatments to prevent a return of schizophrenic symptoms? Do they produce serious or irreversible side effects? How do they work; what is the biochemical mechanism of their action on the brain?

The efficacy of the antipsychotic drugs in the treatment of schizophrenia has been established in numerous clinical trials. The drugs are effective in all subtypes of schizophrenia, at all stages of the illness, at all ages, and in every country where they have been studied (*12*). In the studies that established this efficacy the quantitative, double-blind, controlled research method was used. In this design, symptoms are quantitated by having one or more psychiatrists rate a patient's symptoms on standardized rating scales after a daily interview. The studies are double-blind in that both the investigator and the patient are unaware of what the patient is receiving, and they are controlled because one or more drugs are compared to a medically inert placebo or to a drug with known efficacy.

Figure 2 summarizes some of the results of an NIMH collaborative study of the efficacy of the treatment of acute schizophrenia with antipsychotics (*13*). Approximately three-fourths of patients were "much improved" by antipsychotics during the 6-week study, while nearly half of the placebo group were "worse." Double-blind, controlled studies have also been used to determine the efficacy of maintenance antipsychotic drugs in preventing the return of schizophrenic symptoms after an initial response to treatment.

A recent review summarized the 24 studies that met criteria for appropriate design (*14*). It was reported in this review that 698 of 1068 patients (65 percent) who received a placebo relapsed, compared to 639 of 2127 (30 percent) receiving maintenance antipsychotics; thus, the relapse rate in the drug-treated group was less than half that in the placebo group. Two conclusions can be drawn from this review of maintenance treatment. First, maintenance antipsychotics can prevent relapse in many but not all patients with schizophrenia. Second, since some patients do not relapse on placebo, these patients do not require maintenance treatment. Unfortunately, although some progress has been made, it is still not possible to predict with certainty which patients will relapse. The urgency of such a prediction is increased by several reversible but troublesome side effects, and by the one potentially irreversible side effect, caused by antipsychotics.

Antipsychotics are relatively safe, but they occasionally do produce troublesome side effects. Extrapyramidal motor reactions is the general term given to a wide variety of muscle or movement side effects sometimes caused by these medications. Some patients experience uncontrollable restlessness or muscle spasms in the neck, trunk, or eyes. Others develop muscle side effects that resemble the symptoms of Parkinson's disease, such as muscle rigidity, tremors, altered posture, and shuffling gait. Most of these extrapyramidal muscle reactions occur soon after antipsychotics are started and usually disappear spontaneously. They can also be controlled by the anticholinergic drugs that are used to treat Parkinson's disease (*12*).

Tardive dyskinesia is a movement disorder that is distinct from the early extrapyramidal reactions in several ways. It usually occurs only after prolonged treatment with antipsychotics. It does not usually respond to anticholinergic medications, and it is sometimes irreversible. Tardive dyskinesia consists of frequent, repetitive, involuntary movements of the lips, tongue, jaw, face, and sometimes of the trunk or limbs. These movements can be socially embarrassing and can make speech, eating, and sometimes even breathing difficult (*15*). The reported prevalence of tardive dyskinesia in hospitalized patients with mental illness varies between 0.5 and 40 percent, with a mean of about 15 percent (*16*). Differences in methods of case finding and definitions of the disorder make it difficult to accurately determine prevalence. However, the possibility that a patient will develop tardive dyskinesia makes the decision to place him on maintenance antipsychotics extremely difficult. The risk of and potential for life disruptions from a relapse of schizophrenic symptoms must be weighed against the risk of tardive dyskinesia.

Some patients probably should not be placed on maintenance antipsychotics. Patients with good social adjustment who develop schizophrenic symptoms suddenly in response to stress usually respond rapidly to antipsychotics and may never develop symptoms again. Hospitalized patients with chronic schizophrenic symptoms that respond only minimally to antipsychotics may not require drug maintenance. The gains from drug therapy in such patients are small. Relapse is not as much of a life problem

Table 1. Dopamine pathways.

Pathway	Anatomic location	Hypothesized roles
Nigrostriatal	Substantia nigra (A9) to caudate-putamen (striatum)	Muscle and movement coordination Parkinson's disease Extrapyramidal symptoms of antipsychotics Animal stereotypy(?) Tardive dyskinesia(?)
Mesolimbic-mesocortical	Substantia nigra and area medial to substantia nigra (A9, A10) to limbic nucleii and cortical regions	Emotional tone(?) Antipsychotic action of neuroleptics(?) Amphetamine and L-dopa psychosis(?) Schizophrenia(?)
Tuberoinfundibular	Arcuate nucleus to median eminence	Modulation of some endocrine functions Antipsychotic drug action on prolactin

as it would be for an employed outpatient, and the risk of tardive dyskinesia is great. However, for many patients the return of schizophrenic symptoms can cause severe life disruptions, and the benefits of maintenance antipsychotics would seem to outweigh the risk of tardive dyskinesia.

Antipsychotics and Brain Chemistry

A considerable body of evidence has accumulated showing that antipsychotic medications act by blocking the receptors of brain neurons that are stimulated by the neurotransmitter dopamine (*17*). Such chemical neurotransmitters are released by a small electrical potential in a neuron. The chemical diffuses across the microscopic gap, the synaptic cleft, that separates one neuron from another. The neurotransmitter then stimulates a receptor in the second neuron, causing it to increase its electrical activity.

Dopamine is presumed to serve as the neurotransmitter in at least three specific pathways in the brain: the nigrostriatal, the mesolimbic-mesocortical, and the tuberoinfundibular pathways (*17, 18*). The anatomic localization and some proposed functions for these pathways are listed in Table 1. Antipsychotic medications block dopamine receptors in all three; nigrostriatal blockade causes the extrapyramidal reactions, tuberoinfundibular blockade causes endocrine changes, and mesolimbic-mesocortical blockade is presumed to yield the antipsychotic activity of the medications (*17*). Seven separate types of evidence support the concept that antipsychotics block dopamine receptors.

1) Antipsychotics increase the turnover (synthesis and breakdown) of dopamine, as demonstrated first by Carlsson and Lindqvist in 1963 (*19*). These investigators suggested that the increased turnover results from a feedback mechanism attempting to overcome dopamine receptor blockade. Increased turnover has also been shown in humans. However, one antipsychotic, clozapine, fails to have the expected effect on dopamine turnover in humans (*20*).

2) All antipsychotics except clozapine cause extrapyramidal reactions that sometimes mimic the symptoms of Parkinson's disease (*21*). Parkinson's disease results from degeneration of the nigrostriatal dopamine pathway, leading to a predominance of cholinergic over dopamine activity in this region (*22*). The similarity of antipsychotic-induced extrapyramidal reactions to the symptoms of Parkinson's disease suggests that antipsychotics inhibit dopamine activity in this nigrostriatal pathway. The improvement of both Parkinson's disease and extrapyramidal symptoms by anticholinergic drugs is further evidence of their similar biochemical mechanisms. The failure of clozapine to produce extrapyramidal reactions may be due to its potent anticholinergic activity (*17*).

3) Antipsychotics counteract the electrical response of neurons to the application of microscopic amounts of dopamine (*23*). The effects of amphetamine on neuronal activity are similar to the effects of dopamine. Antipsychotics also reverse the effects of amphetamine on the electrical activity of neurons (*23*).

4) In animals, antipsychotics reverse the behavioral effects of drugs that alter central dopamine activity. Amphetamine and apomorphine both cause altered behaviors in animals that are thought to be due to increased activity in brain dopamine pathways. These animal behaviors are reversed, blocked, or normalized by antipsychotics (*17, 24*).

5) Antipsychotics inhibit the activity of the enzyme dopamine-sensitive adenylate cyclase. Kebabian *et al.* (*25*) have suggested that this enzyme may be involved in the mechanism of dopamine receptors. Activity of this enzyme is increased in the presence of dopamine and decreased in the presence of antipsychotics. However, some antipsychotics, particularly butyrophenones, are less active against this enzyme than would be predicted from their clinical potency (*17, 25*).

6) Antipsychotics are found to inhibit the binding of dopamine to nerve cell membranes in laboratory preparations made from animal brain homogenates. Studies by Snyder (*26*) and Seeman *et al.* (*27*) suggest that the neurotransmitter may bind to the dopamine receptor in these preparations. The relative potency of antipsychotics in this system closely parallels both their clinical potency and their ability to inhibit dopamine-sensitive adenylate cyclase. Again, the butyrophenones inhibit dopamine binding less well than is predicted from clinical potency. However, all antipsychotics inhibit the binding of the butyrophenone haloperidol to nerve cell membranes, with a potency that parallels their clinical potency (*26*). Snyder (*26*) suggests that dopamine and haloperidol bind to discrete agonist and antagonist states of the dopamine receptor and that displacement of antagonist or haloperidol binding may be a better test of antipsychotic activity.

7) Antipsychotics stimulate the release of the hormone prolactin from the pituitary gland, and the tuberoinfundibular pathway plays a major inhibitory role in the regulation of prolactin release (*17, 28*). Sachar and his associates (*28*) report a close correlation between the prolactin response and the antipsychotic potency of the various chemical classes of antipsychotics.

Thus, there is considerable evidence that antipsychotics block brain dopamine receptors. This evidence led to the hypothesis that dopamine neuronal activity is excessive in schizophrenic patients, possibly in the mesolimbic-mesocortical pathway (*17*). This hypothesis of schizophrenia is supported by other indirect pharmacological evidence, but there is not yet any consistent direct evidence of altered brain dopamine metabolism or activity in schizophrenics (*29*).

Tardive dyskinesia is also thought to result from dopamine hyperactivity, but in the nigrostriatal pathway. The prolonged dopamine receptor blockade could lead to supersensitive receptors causing a relative predominance of dopamine over acetylcholine activity in this region (*30*). This imbalance in tardive dyskinesia would be the opposite of the imbalance in extrapyramidal reactions to antipsychotics and in Parkinson's dis-

ease, where acetylcholine is predominant. Since Parkinson's disease and extrapyramidal reactions respond to anticholinergics, tardive dyskinesia might reasonably respond to increasing acetylcholine activity. In preliminary studies the acetylcholine precursor choline chloride has been found to improve the movements of some patients with tardive dyskinesia (*31*). This finding supports the imbalance hypothesis of tardive dyskinesia and offers a potential treatment strategy for the disorder.

Antidepressant Medications

The two major types of drugs used to treat depression are the tricyclic antidepressants (tricyclics) and the monoamine oxidase inhibitors. Drugs from both pharmacological classes were first introduced in 1957, but monoamine oxidase inhibitors are used much less commonly than are tricyclics—they are generally thought to be less effective and more toxic. Tricyclics take 2 to 4 weeks to alter the symptoms of severe depression, but they are effective in about 70 percent of patients. In most cases tricyclics cause a complete remission of depressive symptoms; they improve mood, restore confidence, relieve the numerous physical symptoms, and eliminate suicidal thinking. Some patients may fail to respond to one tricyclic but will respond to another. In patients who remain depressed after a trial of two tricyclics, the monoamine oxidase inhibitors sometimes reverse depressive symptoms (*32*).

The same questions that were asked about the antipsychotics can be asked about the tricyclics: Are they effective in acute depressions or useful as maintenance treatments when compared to a placebo? Do they have dangerous or irreversible side effects? What is the biochemical mechanism of tricyclic action?

The efficacy of tricyclics in the treatment of depression has been established in numerous clinical trials. In one recent literature review, which summarized only double-blind, placebo-controlled studies, tricyclics were found to be more effective than a placebo in 61 of 93 studies (*33*). The fact that 32 studies did not find tricyclics superior to a placebo may seem surprising. However, this is probably due to the high spontaneous remission rate in depression and the slow action of tricyclics. Mild depressions are more likely to remit spontaneously than severe depressions, but it has been estimated that about 30 percent of patients with severe depression recover without drug treatment. Studies that include patients with mild depression may have a placebo group with a remission rate nearly as high as that of the tricyclic group. Thus, tricyclics are more appropriately used to treat severe depression. Even though some of these patients would recover without drug treatment, the danger of suicide in severe depression makes tricyclic treatment not only important in relieving suffering, but also potentially lifesaving (*32*).

Three major collaborative studies, two in the United States and one in England, have found that tricyclics significantly reduced the relapse rate in patients who were initially treated with them (*34*). Since tricyclics have several potentially troublesome side effects, they probably should not be used as a maintenance treatment after recovery for a patient with a single depressive episode. However, for patients with repeated episodes of severe depression the side effects of tricyclic maintenance seem to be a small risk compared to the suffering and potential for suicide associated with multiple depressive episodes (*32*).

Tricyclics can be fatal when a large overdose is taken. This is an unfortunate characteristic for a drug used for the treatment of illness that can lead to suicide. Standard doses of tricyclics also cause several troublesome side effects, but they are usually not dangerous, except in patients with heart disease. Rarely, tricyclics can precipitate mania or schizophrenia in patients with a history of these illnesses. Tricyclics do not seem to cause the extrapyramidal motor reactions seen with the antipsychotics. Perhaps most importantly, tricyclics do not seem to cause tardive dyskinesia. Thus, the decision to place a patient on a maintenance drug is less complicated with tricyclics than with antipsychotics, except in patients with concurrent heart disease (*32*).

Despite an impressive quantity of data accumulated over the last 20 years, the exact mechanism of action of tricyclics is unknown (*32*). The most important hypothesis is that tricyclics increase the functional activity of the brain neurotransmitters norepinephrine and serotonin. Tricyclics are thought to potentiate norepinephrine and serotonin by preventing their uptake by the neuron that released them into the synaptic cleft. Their reuptake prevents these chemicals from continuing to act on the receptor on the second neuron and thus is one physiological mechanism for deactivating them. Reuptake blockade therefore should increase the concentration of norepinephrine and serotonin at the receptor (*35*). Reuptake blockade as a mode of action of tricyclics is suggested by numerous studies which show that these drugs inhibit the uptake of norepinephrine or serotonin injected into the rat brain (*35*).

The reuptake blockade of tricyclics forms part of the basis of the norepinephrine and serotonin hypothesis of affective disorders. This hypothesis, which is supported by several pharmacological and physiological findings, states that depression is due to a functional underactivity or deficiency of these neurotransmitters, while mania is associated with their functional hyperactivity (*35*). The other major class of antidepressants inhibits the action of the enzyme monoamine oxidase, which breaks down norepinephrine and serotonin, and thus monoamine oxidase inhibitors should also increase the concentration of the neurotransmitters (*36*). Reserpine is used to treat hypertension; it depletes brain norepinephrine and serotonin and causes a "depressionlike" syndrome in some patients. Some depressed patients seem to excrete lower amounts of 3-methyoxy-4-hydroxyphenylglycol, the most important breakdown product of norepinephrine. [Others have low spinal fluid concentrations of 5-hydroxyindoleacetic acid, the major metabolite of serotonin (*35*)]. Some depressed patients also have specific abnormalities in endocrine systems that are controlled by the hypothalamus and the pituitary gland (*37*). Hypothalamic-pituitary function also seems to be influenced by serotonin and norepinephrine activity (*38*).

Thus, there is some evidence that decreased norepinephrine or serotonin is associated with depression, but the hypothesis cannot be considered to be established. Much of the evidence is controversial. The true mechanism of action of either the monoamine oxidase inhibitors or the tricyclics is not known. Reserpine does not cause a depression-like syndrome in everyone, and the similarity between this syndrome and clinical depression is the subject of debate. Not every depressed patient has low excretion of 3-methoxy-4-hydroxyphenylglycol, low concentrations of 5-hydroxyindoleacetic acid in the spinal fluid, or specific endocrine abnormalities (*37*).

A major problem for the norepinephrine-serotonin hypothesis of depression comes from the actions of tricyclics themselves. These medications immediately cause neurotransmitter reuptake blockade in animal studies, but they take 2 to 4 weeks to have antidepressant action in patients. The long-term effects of tricyclics on norepinephrine and serotonin are difficult to study and may not

be the same as short-term ones. In addition, iprindole is an effective tricyclic that has been used in Europe and that does not seem to inhibit reuptake of norepinephrine or serotonin (*37, 39*). Thus, neither the biochemical basis of depression nor the mechanisms of action of antidepressants are known with certainty. The reuptake blockade of norepinephrine and serotonin by tricyclics and the norepinephrine-serotonin hypothesis of depression may be oversimplifications, but both hypotheses have helped organize important research on the biochemistry of the brain. More recent hypotheses of depression and of the biochemical mechanisms of tricyclics suggest an altered balance between the functional activities of two or more neurotransmitters, the possible involvement of acetylcholine in depression, and the hypothesis that depression and the action of tricyclics are the result of alterations in neurotransmitter receptors rather than the neurotransmitters themselves (*37*).

Lithium Carbonate

The discovery by John Cade in Australia in 1949 that lithium salts are effective antimanic agents marked the advent of modern psychopharmacology. Curiously, the drug was not introduced into the United States until 1969. Lithium is a unique drug for several reasons. It is highly specific in relieving manic symptoms—normalizing mood and slowing down thinking, motor activity, and other behaviors—all without causing oversedation. In addition, lithium seems to prevent or decrease the severity of both manic and depressive episodes in some bipolar patients. Finally, the lithium compounds used are simple inorganic salts that have no known function in normal physiology (*40*).

The efficacy of lithium in treating acute mania has been established in at least ten controlled studies (*41*). In general, these studies showed that lithium has more specific or unique effects in manic patients than do antipsychotics. However, lithium takes 4 to 10 days to begin to reduce manic symptoms. Thus, for some severely hyperactive and agitated patients with mania, the sedative and tranquilizing effects of the antipsychotics are necessary for 1 or 2 weeks (*41*).

Eight controlled, blind studies have shown that maintenance lithium either prevents or decreases the number of manic episodes in bipolar patients (*42*). Lithium also seems to prevent or decrease the number of depressive episodes in bipolar patients, and may prevent depressive episodes in some patients with severe recurrent unipolar depression (*34*). Since tricyclics also prevent depressive episodes in unipolar depressed patients and are the current treatment, controlled trials comparing lithium and tricyclics as maintenance treatments in unipolar depressed patients are urgently needed.

Unlike the antipsychotics and tricyclics, lithium seems to have a narrow range of effective concentrations in blood. Therefore, blood levels of lithium are measured frequently at first, but as the dose is established the interval between measurements can be extended to weeks or even months. Lithium can have numerous troublesome side effects on many organ systems, but most of these occur early in treatment, and no long-term or permanent side effects have been reported (*40*).

The biochemical mechanism of action of lithium on the brain is unknown. Lithium is distributed throughout the body and interacts with numerous biological systems, including the brain neurotransmitters norepinephrine and serotonin. The norepinephrine hypothesis of affective disorders proposes a norepinephrine overactivity in mania. Lithium decreases the electrically stimulated release of norepinephrine and seems to enhance its reuptake from the synaptic cleft (*37, 43*). This action is opposite to that of the tricyclics, and could explain the effect of lithium on mania. However, any biochemical hypothesis of the action of lithium must also explain its positive effect in some depressed patients (*37*). Thus, further studies of both the short- and long-term effects of lithium are needed to help clarify its mode of action.

Ethics and Psychopharmacology

Among the many ethical issues surrounding the use of psychotherapeutic agents, involuntary treatment is a particular subject of debate both within and outside the psychiatric profession. Should patients ever be given drug treatments without their consent? The exact legal mechanism varies, but severely disturbed patients often do receive such treatment. In California, patients must be a danger to themselves, a danger to others, or gravely disabled as a result of mental illness (*44*). Those who meet these criteria are often depressed patients with suicidal intentions or schizophrenic patients who are violent or unable to care for their basic needs.

Some argue that this involuntary treatment, although well intentioned, alters behavior by external means and that patients should have a right to refuse such treatment even when they are mentally ill (*45*). Szasz (*46*), an articulate spokesman for this viewpoint, believes that the government and the mental health profession have joined together, as did the state and the church in the past, to force people to conform to certain behaviors and beliefs (*45*). Szasz believes that individuals should be free to determine their own behavior, their own beliefs, and their own future, even if this behavior is potentially dangerous to the individual or to society. The logical consequence of this belief is that mental patients have the same rights and responsibilities as other members of the community. A psychiatric patient who harms someone should be tried and held responsible even if the action was due to a mental illness. Szasz's viewpoint has other logical consequences that are difficult for many people to accept. For instance, it suggests that a depressed patient should be allowed to commit suicide and a schizophrenic patient should be allowed to die from dehydration if he feels that fluids are poisoned (*1*).

In practice, many people feel that it is more humane to treat some patients without their consent. Suicidal feelings and delusional beliefs usually are temporary and respond to drug treatment. Patients are often grateful that their transient self-destructive or dangerous behavior was stopped. Suicidal thoughts and delusions are powerful controls over a person's behavior. Involuntarily treatment can remove these emotions and thus can be seen as liberating rather than restricting, since they can allow patients to return rapidly to their former lives, free of dangerous behaviors and self-destructive impulses (*1*).

There is no simple solution to the ethical dilemma of involuntary treatment. When used inappropriately, involuntary treatment can become one of the instruments a totalitarian state uses to control deviant behavior. When used in a humane manner, it can be lifesaving. Clearly, ethical inquiry must play a larger role in psychiatric treatment than it has in the past.

Conclusion

Remarkable progress has been made in the drug treatment of psychiatric dis-

orders. Psychopharmacological agents are the cornerstone of the vastly improved mental health treatment structure for patients with schizophrenia, depression, and mania. The medications have also prompted psychiatrists to become more rigorous and quantitative in the diagnosis and longitudinal assessment of mental disorders. Perhaps most importantly, psychopharmacological agents have provided an interface between psychiatry and modern biological sciences. This has led to laboratory and clinical research that has improved our understanding of the human brain and of behavior and that offers hope for understanding the biochemical substrates of mental illness.

The pharmacotherapies themselves are far from ideal. Antipsychotics improve schizophrenic symptoms, but do not often "cure" the disease. Maintenance antipsychotics reduce the likelihood of a return of schizophrenic symptoms but add the risk of the sometimes irreversible movement disorder, tardive dyskinesia. Tricyclics do not seem to cause irreversible side effects and often reverse depressive symptoms, but they work slowly and are ineffective in 20 to 30 percent of patients. Tricyclics also can be fatal if taken in sufficiently large doses. Lithium salts can markedly improve the life of a manic-depressive patient, but they have troublesome side effects and do not help all patients. Thus, more effective and less toxic medications are an important goal of research in psychiatry. The combination of basic laboratory studies and carefully designed clinical evaluations is urgently needed to develop and test new medical treatments for mental illness.

Psychotherapeutic drugs are not a panacea. They allow a large number of psychiatric patients to be discharged, sometimes to communities that are poorly prepared to receive them and to provide the continuing care that many patients require. Further efforts are needed to determine the best ways to care for formerly hospitalized individuals and to help them become happy and productive members of society. Too often physicians rely solely on medications when psychological and socioenvironmental treatments are needed. Finally, the existence of potent psychotherapeutic drugs will continue to present ethical challenges to society.

References and Notes

1. P. A. Berger, B. Hamburg, D. A. Hamburg, *Daedalus* **106**, 261 (1977); J. Barchas, P. Berger, R. Ciaranello, G. Elliott, in *Psychopharmacology: From Theory to Practice*, J. D. Barchas, P. A. Berger, R. D. Ciaranello, G. R. Elliott, Eds. (Oxford, New York, 1977), p. 527.
2. F. J. Ayd, Jr., *Discoveries in Biological Psychiatry* (Lippincott, Philadelphia, 1970), p. 230.
3. E. L. Bassuk and S. Gerson, *Sci. Am.* **238**, 46 (February 1978).
4. M. Greenblatt, in *Psychopharmacology: A Generation of Progress*, M. A. Lipton, A. DiMascio, K. F. Killam, Eds. (Raven, New York, 1978), p. 1179.
5. M. Greenblatt, *N. Engl. J. Med.* **296**, 246 (1975).
6. R. Reich, *Bull. N.Y. State Dist. Branches Am. Psychiatr. Assoc.* **15**, 6 (1972).
7. F. N. Arnhoff, *Science* **188**, 1277 (1975).
8. L. C. Wynne and M. T. Singer, *Arch. Gen. Psychiatry* **9**, 191 (1963); S. Arieti, in *Psychopathology of Schizophrenia*, P. H. Hoch and J. Zubin, Eds. (Grune & Stratton, New York, 1966), p. 37; R. Cancro, *Dis. Nerv. Syst.* **29**, 846 (1968); W. T. Carpenter, J. Strauss, S. Maleh, *Arch. Gen. Psychiatry* **28**, 847 (1973); H. E. Lehmann, in *Comprehensive Textbook of Psychiatry*, A. M. Freedman, H. I. Kaplan, B. J. Sadock, Eds. (Williams & Wilkins, Baltimore, ed. 2, 1975), p. 890.
9. H. M. Babigian, in *Comprehensive Textbook of Psychiatry*, A. M. Freedman, H. I. Kaplan, B. J. Sadock, Eds. (Williams & Wilkins, Baltimore, ed. 2, 1975), p. 860; H. E. Lehmann, in *ibid.*, p. 851.
10. J. M. Mendels, *Concepts of Depression* (Wiley, New York, 1970); G. R. Klerman, in *Comprehensive Textbook of Psychiatry*, A. M. Freedman, H. I. Kaplan, B. J. Sadock, Eds. (Williams & Wilkins, Baltimore, ed. 2, 1975), p. 1003; F. F. Flach and S. C. Draghi, *The Nature and Treatment of Depression* (Wiley, New York, 1975); G. Usdin, *Depression: Clinical Biological and Psychological Perspectives* (Brunner/Mazel, New York, 1977); W. E. Fann, I. Karacan, A. D. Pokorny, R. L. Williams, Eds., *Phenomenology and Treatment of Depression* (Spectrum, New York, 1977).
11. N. Kline, *Dis. Nerv. Syst.* **37**, 10 (1976).
12. R. I. Shader and A. H. Jackson, in *Manual of Psychiatric Therapeutics*, R. Shader, Ed. (Little, Brown, Boston, 1975); p. 63; J. O. Cole, in *Drug Treatment of Mental Disorders*, L. Simpson, Ed. (Raven, New York, 1976), p. 13; L. E. Hollister, in *Psychopharmacology: From Theory to Practice*, J. D. Barchas, P. A. Berger, R. D. Ciaranello, G. R. Elliott, Eds. (Oxford, New York, 1977), p. 121.
13. J. Cole, S. Goldberg, G. Klerman, *Arch. Gen. Psychiatry* **10**, 246 (1964); R. F. Prien and J. Cole, *ibid.* **18**, 482 (1968); J. M. Davis, *Am. J. Psychiatry* **133**, 208 (1976).
14. J. M. Davis, *Am. J. Psychiatry* **132**, 1237 (1975).
15. E. G. DeFraites, K. L. Davis, P. A. Berger, *Biol. Psychiatry* **12**, 267 (1977); R. J. Baldéressarini and D. Tarsy, in *Psychopharmacology: A Generation of Progress*, M. A. Lipton, A. DiMascio, K. F. Killam, Eds. (Raven, New York, 1978), p. 993.
16. W. E. Fann, J. M. Davis, D. S. Janowsky, *Dis. Nerv. Syst.* **33**, 182 (1972); R. J. Baldessarini, *Can. Psychiatr. Assoc. J.* **19**, 551 (1974).
17. P. A. Berger, G. R. Elliott, J. D. Barchas, in *Psychopharmacology: A Generation of Progress*, M. A. Lipton, A. DiMascio, K. F. Killam, Eds. (Raven, New York, 1978), p. 1071; A. Carlsson, *Am. J. Psychiatry* **135**, 164 (1978).
18. U. Ungerstedt, *Acta Physiol. Scand. Suppl. 367* (1971), pp. 1–48.
19. A. Carlsson and M. Lindqvist, *Acta Pharmacol. Toxicol.* **20**, 140 (1963).
20. J. Gerlach, K. Thorsen, R. Fog, *Psychopharmacologia* **40**, 341 (1975).
21. H. R. Bürki, E. Eichenberger, A. C. Sayers, T. C. White, *Pharmakopsychiatr. Neuro Psychopharmakol.* **8**, 115 (1975).
22. O. Hornykiewicz, *Klin. Wochenschr.* **75**, 309 (1963).
23. B. S. Bunney and G. K. Aghajanian, in *Predictability in Psychopharmacology: Preclinical and Clinical Correlations*, A. Sudilovsky, S. Gershon, B. Beer, Eds. (Raven, New York, 1975), p. 225.
24. J. D. Barchas, P. A. Berger, S. Matthysse, R. J. Wyatt, in *Principles of Psychopharmacology*, W. G. Clark and J. del Guidice, Eds. (Academic Press, New York, in press).
25. J. W. Kebabian, G. L. Petzgold, D. Greengard, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 2145 (1972).
26. S. H. Snyder, *Am. J. Psychiatry* **133**, 197 (1976).
27. P. Seeman, M. Chou-Wong, J. Tadesco, K. Wong, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 4376 (1975).
28. E. J. Sachar, P. H. Gruen, N. Altman, G. Langer, F. S. Halpern, M. Liefer, in *Neuroregulators and Psychiatric Disorders*, E. Usdin, D. A. Hamburg, J. D. Barchas, Eds. (Oxford, New York, 1977), p. 242.
29. J. D. Barchas, P. A. Berger, G. R. Elliott, E. Erdelyi, R. J. Wyatt, in *Biochemistry and Function of Monoamine Enzymes*, E. Usdin, N. Weiner, M. B. H. Youdin, Eds. (Dekker, New York, 1977), p. 863.
30. H. L. Klawans, Jr., *Am. J. Psychiatry* **130**, 82 (1973); K. L. Davis, L. E. Hollister, P. A. Berger, J. D. Barchas, *Psychopharmacol. Commun.* **1**, 533 (1975).
31. K. L. Davis, L. E. Hollister, P. A. Berger, *N. Engl. J. Med.* **293**, 152 (1975); K. L. Davis, L. E. Hollister, J. D. Barchas, P. A. Berger, *Life Sci.* **19**, 1507 (1976); J. H. Growdon, M. J. Hirsch, R. J. Wurtman, W. Wiener, *N. Engl. J. Med.* **297**, 524 (1977); K. L. Davis and P. A. Berger, *Biol. Psychiatry* **13**, 23 (1978).
32. J. J. Schildkraut and D. F. Klein, in *Manual of Psychiatric Therapeutics*, R. I. Shader, Ed. (Little, Brown, Boston, 1975), p. 39; J. M. Davis, in *Drug Treatment of Mental Disorders*, L. Simpson, Ed. (Raven, New York, 1976), p. 127; P. A. Berger, in *Psychopharmacology: From Theory to Practice*, J. D. Barchas, P. A. Berger, R. D. Ciaranello, G. R. Elliott, Eds. (Oxford, New York, 1977), p. 174.
33. J. B. Morris and A. T. Beck, *Arch Gen. Psychiatry* **30**, 667 (1974).
34. J. M. Davis, *Am. J. Psychiatry* **133**, 1 (1976).
35. J. J. Schildkraut, *ibid.* **122**, 509 (1965); W. E. Bunney and J. M. Davis, *Arch. Gen. Psychiatry* **13**, 483 (1965); P. A. Berger, in *Neurotransmitter Function*, W. S. Fields, Ed. (Grune & Stratton, New York, 1977), p. 305.
36. P. A. Berger and J. D. Barchas, in *Psychotherapeutic Drugs*, E. Usdin and I. S. Forrest, Eds. (Dekker, New York, 1977), p. 1173.
37. ———, in *Psychopharmacology: From Theory to Practice*, J. D. Barchas, P. A. Berger, R. D. Ciaranello, G. R. Elliott, Eds. (Oxford, New York, 1977), p. 151.
38. P. A. Berger, J. D. Barchas, J. Vernikos-Danellis, *Nature (London)* **248**, 424 (1974); B. S. Carroll and J. Mendels, in *Hormones, Behavior and Psychopathology*, E. J. Sachar, Ed. (Raven, New York, 1976), p. 193.
39. S. B. Ross, A. L. Renyi, S. O. Ogren, *Life Sci.* **10**, 1267 (1971); M. H. Bickel, in *Psychotherapeutic Drugs*, E. Usdin and I. S. Forrest, Eds. (Dekker, New York, 1977), p. 1131.
40. R. R. Fieve, in *Drug Treatment of Mental Disorders*, L. Simpson, Ed. (Raven, New York, 1976), p. 193; R. L. Sack and E. DeFraites, in *Psychopharmacology: From Theory to Practice*, J. D. Barchas, P. A. Berger, R. D. Ciaranello, G. R. Elliott, Eds. (Oxford, New York, 1977), p. 208.
41. S. Gershon, in *Psychotherapeutic Drugs*, E. Usdin and I. S. Forrest, Eds. (Dekker, New York, 1977), p. 1377.
42. F. Quitkin, A. Rifkin, D. Klein, *Arch. Gen. Psychiatry* **33**, 337 (1976).
43. S. M. Schanberg, J. J. Schildkraut, I. J. Kopin, *Biochem. Pharmacol.* **16**, 393 (1967); R. I. Katz, T. N. Chase, I. J. Kopin, *Science* **162**, 466 (1968).
44. The California Community Mental Health Services Act (Lantermann-Petris-Short Act), division 5, part I, chaps. 1, 2, and 3.
45. T. A. Gonda and M. B. Waitzkin, *Curr. Concepts Psychiatry* **1**, 5 (1976).
46. T. Szasz, *Law, Liberty, Psychiatry* (Macmillan, New York, 1963).

47. I thank J. D. Barchas, G. R. Elliott, and S. I. Watson for helpful discussions and J. S. Magliozzi for manuscript preparation. Supported by National Institute of Mental Health Specialized Research Center grant MH-30854 and the Medical Research Service of the Veterans Administration.