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EDITORS

Harold I. Kaplan, M.D.

Professor of Psychiatry, New York University School of Medicine
Attending Psychiatrist, University Hospital of the New York University Medical Center
Attending Psychiatrist, Bellevue Hospital, New York, New York

Benjamin J. Sadock, M.D.

Professor and Vice Chairman, Department of Psychiatry,
New York University School of Medicine,
Attending Psychiatrist, University Hospital of the New York University Medical Center;
Attending Psychiatrist, Bellevue Hospital, New York, New York

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Editor: Sara A. Finnegan
Associate Editor: Victoria M. Vaughn
Design: Joanne Janowiak
Development Editor: Anne D. Craig
Illustration Planning: Lorraine Wrozsek
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CHAPTER 17 SCHIZOAFFECTIVE DISORDERS

SAMUEL B. GUZE, M.D.

INTRODUCTION

The third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) provides no definition for schizoaffective disorders, nor does it provide diagnostic criteria. The category is included among Psychotic Disorders Not Elsewhere Classified to indicate strong reservations about its validity as a separate disorder. Experienced clinicians recognize, however, that certain patients present with a mixture of affective and psychotic features, especially early in the course of their illnesses, that suggest either schizophrenia or a major affective disorder, but a confident differential diagnosis is not possible. Usually, the clinical course ultimately permits a diagnosis of either schizophrenia or affective disorder in these patients, but when first seen, a diagnosis of schizoaffective disorder is frequently made to indicate uncertainty while defining the diagnostic problem. Obviously, implicit in any effort to distinguish among schizophrenic, affective, and schizoaffective disorders is the assumption that the distinction has validity; that is, that the classification is associated with some significant differences in clinical course, response to treatment, outcome, familial illness patterns, cause, or pathogenesis.

HISTORY AND DEFINITION Ever since Kraepelin's work on dementia precox, debate about the concept and definition of schizophrenia has interested psychiatrists. For some psychiatrists, persuaded by Kraepelin, the diagnosis of schizophrenia should be reserved for a relatively narrow group of psychotic patients whose general prognosis, both clinical and social, is poor. For other psychiatrists, who follow Bleuler's views, the diagnosis of schizophrenia includes a wider range of patients with variable prognoses. It is somewhat paradoxical, however, to note that Kraepelin claimed that about 10 to 15 percent of his schizophrenic patients recovered completely, whereas Bleuler insisted that none of his patients ever returned fully to their premorbid state.

As a result of these differences in perspective, psychiatrists influenced by Kraepelin sought to identify diagnostic criteria associated with a generally poor prognosis and have defined schizophrenia accordingly. Emphasis has focused on the insidious onset of the disorder, the schizoid prepsychotic personality, the absence of obvious precipitating life events, the restricted affect, the tendency to a celibate life, the inability to establish oneself in a career, and the increased familial prevalence of similar illnesses.

As noted, psychiatrists influenced by Bleuler adopted a much broader view of schizophrenia. The diagnosis of schizophrenia was made whenever patients showed a functional psychotic illness. Bleuler emphasized certain primary symptoms—autistic thinking, ambivalence, certain affective disturbances—that he believed were always present in schizophrenic patients. He assigned delusions and hallucinations to a secondary role, thus making it possible to make the diagnosis of schizophrenia in patients showing few, if any, unequivocal psychotic features.

Psychoanalysts went one step further. By emphasizing a defective ego as the hallmark of schizophrenia, they were ready to include a still broader range of psychopathology in the diagnostic category.

It is easy to understand, therefore, that major differences became evident in the way that the diagnosis of schizophrenia was made. Such opposing views even led to striking national differences: most Western European authorities used a narrow definition, in keeping with Kraepelinian practices, whereas most Americans used a broad definition, in keeping with the Bleulerian and psychoanalytic approaches.

Attempts to clarify these opposing views have been reported during the course of the past 45 years. An early leader in these efforts was Langfeldt, who studied patients resembling more narrowly defined schizophrenics whose long-term course and prognosis, however, suggested that they were not typical Kraepelinian schizophrenics. Langfeldt referred to such disorders as schizophreniform and emphasized their relatively good prognosis and response to treatment. Since then, many investigators have worked on the classification of psychotic patients according to their long-term course and prognosis. As a result, nondemented psychotic patients may be usefully divided into two broad groups, one with a relatively poor prognosis and the other with a relatively good prognosis. Such diagnostic terms as chronic schizophrenia, process schizophrenia, nuclear schizophrenia, and nonremitting schizophrenia have been applied to the former cases, and such terms as acute schizophrenia, remitting schizophrenia, reactive schizophrenia, schizophreniform disorders, and schizoaffective disorders have been applied to the latter cases. Some psychiatrists have argued that these prognostic differences, although valid, do not represent fundamentally different disorders; other psychiatrists have concluded that the differences reflect different basic conditions.

Intercurrent affective syndromes develop in patients suffering from long-established schizophrenia, but such patients are excluded here from the category of schizoaffective disorders, because such affective disturbances apparently do not have the same significance as affective symptoms that precede or develop concurrently with a psychotic syndrome or that appear soon after the acute psychosis has subsided.

Schizoaffective disorders are defined here as syndromes of depressive or manic features that develop before or concurrently with certain psychotic symptoms, such as a preoccupation with a mood-incongruent delusion or hallucination, or that begin immediately after the acute psychotic symptoms remit. The psychotic symptoms are such as to be considered unusual in an uncomplicated affective disorder. If the illness is due to any organic mental disorder, the diagnosis of schizoaffective illness is not made.

Two kinds of psychotic symptoms are included in schizoaffective disorders. The first kind includes symptoms that are part of the criterion list for schizophrenia, such as delusions of control and certain types of auditory hallucinations, and that would suggest schizophrenia, if there were no accompanying affective syndrome. The second kind includes symptoms that arise in the context of an affective syndrome without an apparent relationship to depression or elation. Otherwise, the clinical features consist of various mixtures of affective and schizophrenia-like symptoms.

EPIDEMIOLOGY

Few data are available concerning the prevalence and epidemiological distribution of schizoaffective disorders. Most population surveys of the incidence or prevalence of psychotic disorders have ignored the distinctions discussed here and have tended to include nondemented psychotic patients in the schizophrenia category. Those investigators who have included some psychotic persons in the affective disorder category have generally done so on the basis of unspecified clinical judgment, rather than on the basis of explicit criteria.

Certain observations are pertinent, however, and permit some tentative conclusions. Most patients with depression who consult psychiatrists do not report psychotic symptoms. Probably no more than one-quarter to one-third of such depressed patients experience hallucinations, delusions, or prominent ideas of reference. Such psychotic features probably increase the likelihood of consulting a psychiatrist, so that the percentage of depressed persons with psychotic features included in the over-all group of depressed persons is most likely significantly less than the percentage seen by psychiatrists. At most, an estimated 5 to 10 percent of the persons seeking any professional help have both depressive and psy-

chotic symptoms. The percentage is probably even lower, perhaps between 2 and 5 percent, among persons who never seek professional help, because this group includes many with mild and brief depressions.

The lifetime general population risk for depression has been estimated to be between 5 and 20 percent, depending on the diagnostic criteria and sampling methods that are used. Taking the above estimates for the frequency of psychotic features in depression, one may conclude that a maximum of somewhere between 0.1 percent and 1.0 percent of the population experience a depression with psychotic features.

Combining the estimated prevalence of manic disorders—0.2 percent—with the estimated percentage of manic patients who show psychotic features—about 50 to 70 percent—the population prevalence of mania with psychosis may be estimated at about 0.1 percent.

Most population studies place the prevalence of schizophrenia at less than 1 percent. Most schizophrenics experience affective syndromes sometime during the course of illness, so that an estimate of the association of schizophrenia and affective syndromes, usually depressive, is about 0.5 percent of the population.

If the estimated frequencies of depression with psychotic features, mania with psychotic features, and schizophrenia with affective syndromes are combined, a total estimated frequency of between 0.7 and 1.6 percent is obtained. The estimate of 1.6 percent may be considered the approximate maximum frequency of schizoaffective conditions. The frequency of schizoaffective illness as defined in DSM-III, however, is almost certainly considerably less, because intercurrent affective episodes during the course of schizophrenia are excluded, as are many patients whose psychotic features seem clearly part of an affective illness. Therefore, a reasonable estimate of the prevalence of schizoaffective disorders, as defined here, does not exceed 1 percent.

A major justification for separating schizoaffective disorders from schizophrenia is the difference in the associated familial illness patterns. Close relatives of patients with schizoaffective disorders tend to show a lower prevalence of schizophrenia than is seen in relatives of schizophrenics; instead, the relatives of patients with schizoaffective disorders tend to show a frequency of affective illness similar to that seen in the relatives of patients with affective disorders.

Differential patterns of psychiatric illness in close relatives constitute one of the most important parameters for validating diagnostic categories. Regardless of the relative importance of genetic and environmental factors, nearly all psychiatric disorders have been found to be familial. Thus, finding an increased prevalence of the same disorder among close relatives provides strong support for the validity of any particular diagnosis. When ill, most of the relatives of schizoaffective patients suffer from uncomplicated, straightforward affective illnesses; however, an increased frequency of schizoaffective conditions may be seen among them. Some authors, especially authors reporting the latter increase, have argued that this finding justifies considering schizoaffective disorders as a third functional psychosis, in addition to affective psychosis and schizophrenia. Other authors prefer to consider patients with schizoaffective disorders as a heterogeneous group with varying proportions of depression, mania, and schizophrenia, depending on the method of selecting the samples. The question of a possible third psychosis is usually left unresolved.

No striking sex differences in the frequency of schizoaffective disorders have been reported.

CAUSES

As yet, little is known about the causes of all functional psychoses, including schizoaffective disorders. Evidence for some genetic predisposition to schizophrenic and affective disorders has been obtained from a wide range of pedigree, twin, and adoption studies. Unfortunately, as noted above, relatively little attention has been paid thus far to separating out schizoaffective conditions. It is hardly surprising that most speculation, whether psychodynamic or biological, concerning depressive, schizophrenic, and manic psychopathology has also been applied to schizoaffective conditions.

CLINICAL FEATURES

Patients present with a mixture of affective features, depressive or manic, and one or more hallucinations or delusions that are considered characteristic of schizophrenia or that, because they have no apparent relation to the disordered mood, are unusual in uncomplicated affective disorders.

The psychosis typically begins abruptly, either coincident with an affective disturbance or after an affective syndrome has been present for days or even weeks. Often, it is difficult to be sure which feature was the first to begin. The psychotic and affective components may parallel each other in intensity throughout the illness, or one component may wax and wane while the other one holds steady.

Generally, the psychotic and affective features begin more or less simultaneously; then the hallucinations or delusions subside, leaving the patient with a typical depression or mania. When depression follows, it is frequently described as "postpsychotic depression." The psychotic features are usually dramatic and overt, creating disturbances for relatives, neighbors, and friends.

Episodes may be brief, but usually they last for either weeks or months. Some patients experience repeated episodes, separated by months or years of apparently normal psychological functioning. Other patients have several similar episodes that are followed by other episodes of typical depression or mania. Sometimes these episodes are supplanted by a persistent illness that is indistinguishable from typical chronic schizophrenia, with or without associated periods of disturbed mood.

Suicidal thinking and completed suicide are common in these patients. It is not yet known what proportion of young schizophrenics who commit suicide were suffering from schizoaffective disorders, rather than from uncomplicated schizophrenia. As with the familial illness pattern, the suicide risk suggests to some psychiatrists that many, if not most, schizoaffective illnesses are, in fact, atypical cases of depression or mania, rather than cases of schizophrenia.

COURSE AND PROGNOSIS

The long-term course and outcome of schizoaffective disorders cannot be discussed separately from the course and outcome of schizophrenia itself. The course of schizoaffective disorders is quite variable, but on average, it seems to be significantly better than the course of schizophrenia. The better prognosis applies to the clinical course of the illness and to the social adjustment and appears to be true for untreated patients, as well as for treated ones.

Typically, the psychotic features develop acutely, and the patient comes for professional help within weeks of such onset, because the patient's family or the patient himself recognizes that a significant change in functioning has taken place. The relatively acute onset of the psychotic features has long been recognized as an important favorable prognostic factor. During the psychotic period, it may be difficult to

assess adequately the patient's affective state, although patients usually discuss their moods freely. Sometimes the patient is severely catatonic and is, therefore, inaccessible; but usually such periods are brief, and the patient communicates more freely afterward. Catatonic features may be as evident in schizoaffective disorders as in schizophrenic states.

DIAGNOSIS

The diagnosis of schizoaffective disorders follows directly from their definition and the clinical picture.

PSYCHIATRIC EXAMINATION The psychiatric examination may reveal quite variable findings. In one patient, psychotic features may be more prominent than affective features; in another patient, the situation may be reversed. Yet again, in any single patient, the two types of features may fluctuate together or independently. Usually, the delusions or hallucinations are quite striking and are easy to recognize. Patients are grossly disturbed and create considerable difficulty for their families and friends. In general, the more floridly disturbed the patient, the more there is a likelihood that the illness is schizoaffective, rather than schizophrenic. The affective features are usually similar to the features seen in uncomplicated depression and mania.

DIFFERENTIAL DIAGNOSIS The differential diagnosis includes affective disorders, schizophrenia, organic mental disorders, and certain substance-abuse disorders, particularly those disorders associated with the abuse of lysergic acid diethylamide (LSD), amphetamines, and other hallucinogens.

Substance abuse should always be considered when an acutely psychotic patient is seen, including a patient with striking affective symptoms. Outside history, blood and urine screening for appropriate metabolites, and careful observation frequently permit the correct diagnosis. The majority of substance-abuse illnesses usually subside a few days after discontinuing the drug, and such illnesses rarely last more than 10 to 12 days after the drug has been discontinued.

Some schizoaffective patients show clouding of consciousness early in an episode; therefore, an organic mental disorder must sometimes be seriously considered. Generally, however, the confusion and bewilderment are short-lived and leave the patient with a clear sensorium, despite the continuation of other symptoms. Mild confusion or disorientation may occasionally be evident throughout the illness; in such cases, it may be simply a matter of policy whether the patient receives a diagnosis of schizoaffective disorder or, alternatively, of organic mental disorder.

The major differential diagnostic problems relate to schizophrenia and affective disorders. The history of the concept and the definition of schizoaffective disorders suggest that such patients are a heterogeneous group suffering from schizophrenia, affective disorders, and, possibly, a third functional psychosis. The relative proportions of the mixture probably vary with different circumstances and different diagnostic methods. Also, there is still disagreement as to whether remitting or good-prognosis cases of schizophrenia should be classified as schizophrenia or as affective disorders; to some extent, differential diagnosis is a matter of convention.

Patients with these disorders vary greatly in course and outcome, and a major concern when such patients are first seen is that of estimating prognosis. Efforts to separate patients prospectively into two groups—patients with a relatively good prognosis and a remitting course and patients with a relatively poor outcome and a chronic course—have achieved varied success.

In general, successful efforts to discriminate good-prognosis and poor-prognosis cases have relied on the course of the illness up to the time of study, rather than relying on the clinical picture. A poor prepsychotic life adjustment—manifested by a schizoid personality, few friends, a limited or absent sex life, and an insidious onset of illness, so that it is difficult to tell when the illness began—is the characteristic prognostic feature in poor-prognosis cases. The absence of schizoid personality features or life-style and an acutely developing psychosis, which often seems to have been precipitated by some life event and is usually accompanied by prominent affective symptoms, are the important prognostic features in good-prognosis cases.

Emphasizing the clinical picture, rather than the previous history, has been less successful. Prominent affective symptoms seem to be significant in predicting a remitting course only when seen in the context of an acute psychosis with a good premorbid life history. In the past, when interest in psychiatric diagnosis was more limited, little effort was made to distinguish affective disorders from schizophrenia, so that any patient with psychotic features was simply called schizophrenic. This lack of effort was particularly noted in the United States. As interest in this differential diagnosis has grown, however, patients have been less likely to receive a diagnosis of schizophrenia based simply on the presence of psychotic features. Most affective disorders with psychotic features are recognized as affective illnesses, and in the remaining cases, the presence of affective features alone may not be as helpful in the differential diagnosis.

PSYCHOLOGICAL TESTS

Psychological test results, not surprisingly, show a mixture of features associated with both schizophrenia and affective disorders. Few studies have dealt with schizoaffective disorders as a separate classification.

TREATMENT

Because their psychotic features, affective disturbances, or risk of suicide are generally striking, patients with schizoaffective disorders usually require hospitalization. Antipsychotic agents (such as the phenothiazines and butyrophenones), tricyclic antidepressants, antimanic drugs (such as lithium and the phenothiazines), and electroconvulsive therapy are the mainstays of treatment.

The choice of drug or combination of drugs usually depends on the mixture of clinical features and on the relative severity of the various clinical elements. Patients usually do not respond as well to tricyclic antidepressants alone as they do to antipsychotic drugs, with or without tricyclic antidepressants. Similarly, although lithium alone is sometimes effective, it generally is not as satisfactory as antipsychotic drugs, with or without lithium. Many patients do quite well with pharmacological treatment, but a significant number of patients respond so poorly or so slowly to such treatment that electroconvulsive therapy is recommended.

Most patients have a good response to electroconvulsive therapy. As yet, it is unclear whether such patients are further improved by concomitant drug administration, but many experienced clinicians believe that patients make better progress if the antipsychotic or antimood agent is continued after the electroconvulsive therapy.

Most patients respond to the available treatments. For many, drugs or electroconvulsive therapy or a combination of the two results in prompt recovery and the ability to return to work, school, or home. To what extent the continuation of

an antipsychotic or antimood drug prevents relapse is unclear, but evidence indicates that such a prophylactic effort may be helpful in certain cases. Unfortunately, some patients relapse after only a brief remission and must be treated vigorously to achieve a more lasting remission. A minority of patients show very little improvement, despite the application of all the above-mentioned treatments, and they progress to a chronic state of illness.

SUGGESTED CROSS REFERENCES

The schizophrenic disorders are discussed in Chapter 15, and the affective disorders are discussed in Chapter 18. Drug dependence is discussed in Chapter 22. Examination of the psychiatric patient is discussed in Chapter 12. The organic therapies are discussed in Chapter 30.

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CHAPTER 18 AFFECTIVE DISORDERS

18.1 OVERVIEW OF AFFECTIVE DISORDERS

ROBERT CANCRO, M.D., Med.D.Sc.

INTRODUCTION

The affective disorders constitute a large group of illnesses characterized by alterations of mood. The vast majority of people suffering from affective disorders show an alteration of mood toward depression. Estimates of how many people are depressed in any particular year range widely. Conservative estimates place the number of people who in any given year experience a depressive episode, which is potentially diagnosable, at between 10 and 20 million. In the United States 1 in 20 persons is actually diagnosed as having a significant depression at least once in their lifetime.

DEFINITION

The very term "depression" is in many ways ambiguous. It is used to refer to a mood, a symptom, a syndrome, and possibly even a disease entity. Clearly, the Queen of Hearts did not restrict her authority to the world of Alice, but reigned in the world of clinical nosology as well. All human beings show fluctuations in mood as a reaction to life events. A depressed mood in this sense does not represent a disorder. Obviously, happiness is to be desired, but unhappiness—particularly as an appropriate response—does not constitute a diagnostic category. Unhappiness or normal sadness should not be confused with depression as a syndrome. It would be better in many ways if the mental status examination did not use the term "depression" as a symptom, but replaced it with the term "sadness." Depression as a syndrome or disorder is the only clinically sound usage of the term, and its use should be so restricted.

Just as the mood of an individual can be altered in the direction of depression, so can it be altered in the direction of elation. Elation is an important symptom in that larger constellation called mania. Mania should not be confused with good spirits and a high energy level. Most energetic people do not have a manic disorder, and most manic individuals expend considerable energy, but accomplish very little of value during their manic episodes.

HISTORY Depressive disorders have been recognized and described for as long as history has been recorded. In ancient Egypt for over 3,000 years the depressive disorders were treated by the priests who recognized that depression was often associated with the experience of a psychological loss. King Saul is described in the Old Testament as manifesting recurrent depressive episodes. These descriptions of depression continue in classical Greek literature.

It was not until approximately the 6th century B.C., however, that the observation of the mentally ill began to enter the domain of the healer rather than continuing to be a part of the theological tradition. Before this time madness generally was seen as something inflicted by the gods and, therefore, not subject to rational study. This movement away from theological and philosophical understanding to medical observation reached its flowering in the thought of Hippocrates, who introduced the terms "mania" and "melancholia." His descriptions of melancholia and mania are as clinically valid today as when written. He also attributed the origin of mental illness to natural rather than divine causes. Remarkably, it was Hippocrates who placed mental functions and malfunctions in the brain. He hypothesized that in mental illness the brain was unhealthy as a result of imbalances in the internal humors.

The early Roman physicians also made important contributions to our understanding of the affective disorders. Aretaeus made a distinction between exogenous and endogenous depressions, arguing that although they shared a similar symptomatology they had different origins. He also recognized that mania and depression frequently coexisted in the same individual. He, in fact, argued that mania and melancholia were part of a single disorder and that its origin was related more to the patient's emotional state than to internal humors.

With the Renaissance there was again an emphasis on rational explanations and natural causes for the mental disorders including depression and mania. The role of witchcraft and the influence of the stars became increasingly de-emphasized and was ultimately eliminated. The distinction between the mind and the soul was also helpful in giving natural science a domain separate from that which belonged to theology. Finally, by the 16th and 17th century there was general agreement that the brain was indeed implicated in mental disorders. For the next 200 years there was an increasing emphasis on the humane and enlightened treatment of the mentally ill. The spirit of the French revolution and the age of enlightenment combined with an emphasis on moral treatment to lead increasingly to a more useful approach to all mental disorders including depression and mania.

By the end of the 19th century, Kraepelin separated illogical psychoses without a tendency toward deterioration from illogical psychoses with a tendency toward deterioration. The former group was labeled the manic-depressive psychoses and constitutes the core of what is meant by the affective disorders today. Kraepelin's view was basically organic, but was complemented by the psychoanalytic theories of Freud, Abraham, Rado, and others. The psychoanalytic writers emphasized the role of loss and the turning inward of anger against the introjected object. Freud also emphasized the role of environmental experience and its meaning to the individual in the pathogenesis of depression. More recently, the importance of cognition in depression has been recognized by Beck and his co-workers. Finally, with the advent of the psychopharmacological revolution, biological theories have achieved increasing importance.

CLINICAL DESCRIPTIONS

The subclassification of Affective Disorders utilized by the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) does not follow the model for most other disorders. Affective Disorders are subgrouped into major affective disorders, other specific affective disorders, and atypical affective disorders. The major affective disorders demonstrate a full affective syndrome, whereas the other specific affective disorders show only a partial syndrome of a minimum of 2 year's duration. The atypical group includes those syndromes that cannot be classified into the major and other categories.

The major affective disorders include bipolar disorder and major depression (unipolar). If a manic episode has ever been present, even if a depressive illness has not occurred, the diagnosis of bipolar disorder is made. When bipolar patients show mood swings in the direction of mania and depression, the cycles need not be alternating and, in fact, are very rarely so. Most untreated bipolar individuals have a tendency to show more depressive mood swings than manic episodes.

The other specific affective disorders category includes cyclothymic disorder and dysthymic disorder. Cyclothymic disorder mimics both depressive and manic syndromes, but the severity and duration are not sufficient to meet the criteria

for major affective disorders. In dysthymic disorder the syndrome mimics depression, but the symptoms are neither of sufficient severity nor duration to fulfill the criteria of a major depressive episode.

MANIA The critical clinical feature for a manic episode is a mood that is elevated, expansive, or irritable. The associated symptoms include hyperactivity, pressure of speech, flight of ideas, diminished need for sleep, increased self-esteem to the point of grandiosity, extreme distractibility, short attention span, and extraordinarily poor judgment in the interpersonal and social arenas.

Mania is described in terms of heightened psychomotor activity. The person speaks more rapidly, thinks more rapidly, or moves more rapidly. The person frequently requires much less sleep and has apparently limitless energy. Many people with a manic illness feel that they are highly creative during these attacks. The reason, in part, is because there is a flooding of consciousness with ideas and associations that at times are imaginative and creative but that at other times are idiosyncratic and of little artistic merit. The psychiatric literature often suggests that mania is a condition to be envied rather than treated. This suggestion is clinical nonsense. There are hypomanic periods that are characterized by heightened activity levels and increased productivity. Mania, conversely, is characterized by diminished productivity. The manic patient starts many projects, but finishes few if any of them. Much of the activity is purposeless, and attention is badly fragmented so that there is very little ability to follow through and complete tasks.

Although the elevated mood is often described as euphoric and cheerful and having an infectious quality, it is characterized by an absence of selectivity and an unceasing driven quality. Mania is also characterized by an extremely poor frustration tolerance with resulting heightened irritability. A manic patient may be quite humorous, good natured, and friendly until frustrated in some trivial way. The good humor then promptly disappears and is replaced by anger and even rage. The grandiose expansive quality of the manic episode with the sense of increased power and importance often becomes psychotic in proportion. It is not unusual to find patients in a manic episode thinking that they are God. The grandiosity often provokes social rejection because these patients may show considerable contempt for the people with whom they come into contact.

The increased activity often takes the form of sexual promiscuity, political involvement, and religious concern. The diagnosis can often be made by looking at the patient's phone bill. The patient makes incessant phone calls at all hours of the day and night. Patients in the manic phase are unaware of the social inappropriateness and the intrusive and demanding quality of their behavior. The impaired social judgment and grandiosity can combine to produce buying sprees, bad business decisions, or unwise investments.

The speech of the manic tends to be loud, rapid, uninterruptable, and unceasing. There is often a playing with the sounds of words and the creation of puns and other word games. Dramatic mannerisms are quite common, including bursting into song without apparent provocation or awareness of the inappropriateness of the behavior.

Characteristically, there is a diminished need for sleep, with the patient often functioning at a high energy level on only 3 or 4 hours of sleep. It is also not unusual to see the patient go for several days virtually without any sleep at all.

The manic episode may or may not include psychotic symptoms. The impairment of judgment may not be sufficiently severe to justify a psychotic diagnosis. Delusions and hallucinations are not unusual. The content is usually consistent with the dominant mood. It is quite common for the person to communicate with God and to have it revealed that he or she has a special purpose or mission. Patients frequently describe themselves as an "organ" of God through whom God speaks to the world.

MAJOR DEPRESSIVE EPISODE The essential clinical feature is a dysphoric mood usually experienced consciously as a depression. The disturbance of mood is prominent, persistent, and usually associated with other symptoms as well. Not all individuals, however, who are diagnosed as having a major depressive episode report being subjectively depressed. The symptoms of a severely depressed mood, including feelings of hopelessness, are sufficient for the diagnosis of depression, but are not necessarily present. The symptoms that are necessary for the diagnosis include the triad of reduced capacity to experience pleasure (anhedonia), reduced interest in the environment (withdrawal), and reduced energy (anergia). This triad is of great diagnostic utility and can be utilized even in the absence of demonstrable mood changes. Patients may identify a loss of interest or pleasure in their usual activities as the key features.

There are a number of symptoms that are neither sufficient nor necessary but best thought of as accessory. These symptoms include agitation, weight loss, sleep disturbances, or anorexia. Appetite is frequently disturbed, with loss of appetite being the most common manifestation. When the loss of appetite is significant, there will be weight loss. With children it may take the form of a failure to achieve the expected weight gain. Nevertheless, there are typical cases of major depressive episodes during which patients show increased appetite as a clinical feature. The sleep disturbance most frequently takes the form of either initial insomnia or terminal insomnia; nevertheless, both hypersomnia and middle insomnia are seen. Both psychomotor agitation or psychomotor retardation may be present, but usually only one is found in a given case. Signs of psychomotor agitation include restlessness, pacing, or hand wringing. Psychomotor retardation is best illustrated by a paucity of movement and a slow, almost absent, monotonous speech. A diminished sense of self-esteem is usually present and varies from mild to severe. The patient may show marked guilt feelings over real and imagined past events.

Difficulty in concentrating, calculating, reasoning, and performing complex mental tasks is common. Indecisiveness is quite frequent. Impairment of memory is frequently reported, but seems to be associated with a reduced ability to attend to stimuli rather than to record them. Suicidal ideation and attempts are quite common in major depressive episodes.

EPIDEMIOLOGY

BIPOLAR DISORDER The lifetime risk for bipolar disorder is approximately 1 percent. There are no demonstrable sex differences in the risk for bipolar disease. It tends to occur relatively early in life, with the first attack usually occurring before the age of 30. There is some evidence for an increased rate of bipolar disorder in the upper socioeconomic classes. This finding may be a consequence of the periods of hypomanic activity found in bipolar patients in which the individual can function at an increased level without significant impairment of judgment and thereby achieve higher levels of success. There has been no evidence of a relationship between prevalence and incidence of bipolar disorder and rural-urban

status, marital status, religion, and race. There are no good data available on the role of life events in precipitating manic episodes, although one recent study suggests such a role. The first-degree relatives of bipolar patients show a lifetime risk of 25 percent for an affective disorder.

MAJOR DEPRESSIVE EPISODE The current over-all prevalence for major depressive episodes in the United States is between 3 to 5 percent. The lifetime risk for a major depressive episode seems to be 8 to 12 percent in males and 20 to 26 percent in females. There have been many explanations offered for this striking sex difference. Most studies show at least twice the rate for major depressive episodes in females, but if alcoholism and sociopathy are included in the males, the over-all rate for a major depressive episode, alcoholism, and sociopathy is the same across gender. There has been at least one study among the Amish, who do not suffer from significant problems of alcoholism or sociopathy, that shows no gender difference in the rate of major depressive episodes.

The age of onset for the first major depression is usually by the mid-twenties. There is no increase in the postmenopausal period. There has been no demonstrated relationship between social class and the rate of major depressive episodes. There has also been no relationship shown between race and either the prevalence or the incidence of this disorder. The first-degree relatives of unipolar depressives show a lifetime risk of 20 percent for affective disorder.

GENETICS

BIPOLAR DISORDER A number of twin studies done in the affective disorders are relatively consistent in their findings. The twin method involves the comparison of the concordance rate for the illness in monozygotes with that found in dizygotes. If a genetic factor is operating in the transmission of the disorder, then monozygotes will have a significantly increased concordance rate over that found in dizygotes.

The concordance rate in dizygotes varies between 15 and 20 percent. The concordance rate in monozygotes varies between 67 and 79 percent. There is approximately a 4-fold increase in concordance in monozygotes. This difference is highly significant and, therefore, supportive of a genetic-transmission hypothesis.

The adoption technique has also been applied to the affective disorders. The adoption technique compares the rate of the disorder in both the biological and adoptive relatives of afflicted individuals. If one looks at adoptees who have an affective disorder, the rate of affective disorder in the biological parents is increased by a factor of 3 over that found in the adoptive parents. As many as 31 percent of the biological parents of adoptees with bipolar illness have an affective disorder, compared with 2 percent in controls.

Interestingly, there is evidence to suggest that genetic factors may operate in the vulnerability to suicide. The suicide rate in the biological relatives of affective patients is more than ten times that of a control population.

UNIPOLAR DISORDER The twin method has been applied to unipolar patients as well. The difference between the monozygotic and dizygotic rates is not as striking as that reported in bipolar patients. The monozygotic concordance rate of 54 percent is approximately 2.8 times the dizygotic rate of 19 percent.

The mode of transmission of the predisposition to an affective disorder is unknown. It is generally considered to be polygenic with multiple thresholds. Unfortunately, this genetic explanation is the most common for data that are very noisy and that include several different phenotypic populations, each having a different mode of transmission. There is some evidence from the genetic perspective that alcoholism is linked to major depressive disorders. There is also evidence that the syndrome of anorexia may be linked to affective disorders as well.

SUBTYPING

The recognition that depression and mania are not homogeneous clinical states is not a new one. The efforts to subtype depression have been much more extensive than have been the efforts to subtype mania. The clinical subtyping of affective disorders has been of limited value. Most efforts have involved the use of a dichotomy, such as agitated versus retarded or endogenous versus exogenous. Despite the nosological limitations of these efforts, they have been of some limited clinical utility. The presence of somatic delusions, for example, is a good predictor of a positive response to electroconvulsive therapy (ECT). ECT is also beneficial to patients who show marked retardation, early morning awakening, and vegetative signs. A good response to tricyclic antidepressants is usually associated with an insidious onset of the depressed mood and with vegetative signs, such as anorexia, weight loss, and middle and late insomnia. Many of the depressive features considered atypical respond better to monoamine oxidase inhibitors (MAOI's) than to tricyclic antidepressants.

Despite the clinical utility of these observations, they do not deal with the problem of the need for an improved nosology. It is highly probable that the ultimate nosology of the depressive and manic states will require a deeper understanding of their biology. In the interim, research efforts should continue on a variety of fronts ranging from clinical and epidemiological to biological. Some efforts at subtyping of the depressive disorders are more advanced and will be presented.

CLINICAL SUBTYPING The state-of-the-art in clinical subtyping is reflected in DSM-III. A consensus has developed about the validity and utility of the bipolar category as separate and distinct from other affective disorders. The reliability of the major depressive disorder category also seems to be good. Some observers have argued that a delusional subtype of major depressive disorder should be added. The presence of delusions has important clinical and therapeutic implications. Delusional depression has a higher genetic loading and therapeutically usually requires the addition of a neuroleptic drug or ECT to the antidepressant drug regimen. The presence of delusions also increases the risk for suicide. The use of the subcategories of cyclothymic and dysthymic disorder, atypical bipolar disorder, and atypical depression has less support than the categories of bipolar disorder and major depressive disorder.

BIOCHEMICAL SUBTYPING With the introduction of the psychopharmacological agents in 1957 for the management of depression, interest developed in the basis of their action. It was noted that these compounds affected the metabolism of biogenic amines in the brain. This observation led to the study of these substances and their possible role in the development of the affective disorders. The catecholamine hypothesis states that antidepressant drugs exert their clinical effect by increasing one or another biogenic amine at critical brain receptors. Furthermore, drugs that cause depression or are effective in the treatment of mania have the opposite effect. The early formulations in the etiology of depression gave particular emphasis to the role of the depletion of norepi-

nephrine. Although this hypothesis is obviously a gross oversimplification of the biochemical basis for a heterogeneous syndrome, it has led to much productive research.

The major recent efforts to subtype depressions on the basis of biochemistry have focused on differences in metabolism in unipolar depressions. It is recognized that urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) is a major norepinephrine metabolite originating in the brain. The exact fraction of urinary MHPG derived from the brain is uncertain. Measurements of urinary MHPG may be of value in exploring the pathophysiology of different types of unipolar depression. Some work suggests that there are subtypes of unipolar depressive disorder defined on the basis of differences in urinary MHPG levels. One subtype includes patients who have low MHPG levels and who will probably have a low norepinephrine output. A second subtype includes patients who have intermediate MHPG levels and who may have normal norepinephrine output but difficulties in other neurochemical systems. The third subtype consists of patients who have elevated urinary MHPG levels and who appear to have high norepinephrine output. There are suggestions in the literature that the patients with the high MHPG levels have increased cholinergic activity as a primary abnormality.

ELECTROPHYSIOLOGICAL SUBTYPING Depressed people as a group show electrophysiological differences from normal controls, particularly for general β-measure of the whole head. Depressed patients usually have less β-activity than normals. Depressed patients show considerably less coherency between the left and right hemispheres in the anterior portion of the head. These findings suggest that people diagnosed as having a depressive disorder may show some electrophysiological findings that are consistent and that differentiate them at a statistically significant level from other populations. There have also been some reports of separating unipolar and bipolar depression on the basis of electrophysiological findings. Bipolar patients showed increased β-activity, whereas unipolar patients showed less β-activity than did normal controls.

GENERAL TREATMENT CONSIDERATIONS

The unfortunate schism between psychosocial and biological treatments has tended to result in many patients being treated in a less-than-optimal fashion. There is, in fact, no conflict between these approaches. Virtually all affective disordered patients require both psychosocial and somatic intervention. The patient who responds to a tricyclic antidepressant but does not make appropriate corrections in his or her life-style is at an increased risk for relapse. A strong and supportive social network can have an important prophylactic effect without the dangers of long-term maintenance therapy with an antidepressant.

There are basically two classes of compounds that are pharmacologically active and useful in the treatment of depression. These are the tricyclic antidepressants and the MAOI's. In the United States there has been a marked tendency not to use the MAOI's, but this tendency is a clinical error. Although there are potentially serious problems with the use of these compounds, they are good drugs, particularly for atypical depressions. It is general clinical practice in the United States to start most patients with a depressive disorder on a tricyclic antidepressant. This practice is in some ways unfortunate because individuals who are more likely to respond well to MAOI's or to ECT are not given as early a trial on these treatments as is clinically warranted. Although ECT has a significant social stigma, it remains the safest, most effective, and economically least expensive form of intervention.

Some of the newer compounds, including tetracyclics, offer a better side-effect profile and other clinical advantages over the earlier tricyclic compounds. Nevertheless, the recovery rate in major depressive episodes with these newer compounds is not significantly better than with the earlier tricyclic antidepressants.

Lithium is not only useful for the treatment of acute mania but for its prevention as well. It is also an excellent prophylactic agent for the prevention of depressive mood swings in bipolar patients. The use of lithium is not without danger. In addition to problems of thyroid and renal function, many patients complain of memory impairment with lithium. There is a need for careful cost-benefit analyses of long-term pharmacological prophylaxis. Intermittent rather than continuous use of medication may well be safer in many cases. Care must be taken with the use of neuroleptics and tricyclic antidepressants in bipolar patients. Neuroleptics can produce depressive mood swings, and tricyclics can produce mania.

The addition of carbamazepine to lithium or even its substitution for lithium has been reported to be helpful in many resistant cases, particularly in rapidly cycling bipolar patients. This anticonvulsant is particularly useful in reducing sharp wave activity that can be associated with subcortical kindling.

The affective disorders are a heterogeneous group of illnesses that involve disturbances of mood. The bipolar disorders seem to be genetically and clinically distinct from the unipolar depressions. Nevertheless, the problem of effectively subtyping the affective disorders requires a great deal of additional work. The specificity of the pharmacological treatments in the affective disorders is superior to that found in the schizophrenic disorders, but there is considerable room for improvement. As research gives the field a more meaningful subtyping of the affective disorders, one can expect more discrete and selective treatments that will be increasingly efficacious.

SUGGESTED CROSS REFERENCES

Affective disorders are discussed in this chapter. Schizophrenic disorders are discussed in Chapter 15 and schizoaffective disorders in Chapter 17. Anxiety neurosis is discussed in Section 20.1. Suicide is discussed in Section 28.1. Maternal deprivation is discussed in Section 39.1, and affective disorders in children are discussed in Section 41.10. Suomi discusses ethology in Section 4.6. Classification of mental disorders and DSM-III are discussed in Section 14.1. Epidemiology is discussed in Section 6.1. Alcoholism is discussed in Section 22.3, personality disorders in Chapter 21, and geriatric psychiatry in Chapter 50. Organic therapies are discussed in Chapter 30. Freud's theories are discussed in Chapter 8 and Adolf Meyer's theories in Section 10.2.

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18.2
AFFECTIVE DISORDERS: EPIDEMIOLOGY

MYRNA M. WEISSMAN, Ph.D.
JEFFREY H. BOYD, M.D., M.P.H.

INTRODUCTION

There has been a surge of interest in the epidemiology of psychiatric disorders in the United States that, fortunately, is being followed by a surge of data. Within the next few years, understanding of the magnitude of psychiatric disorders in the United States will be enhanced by the comprehensive study of representative samples of the population, including both treated and untreated persons. (The reader is referred to Regier and associates for a description of the ongoing U.S. Epidemiologic Catchment Area (ECA) study.) The next phase of epidemiology will focus on elucidating the biological, psychological, and social situations; that is, the factors that place certain individuals at greater risk for developing a specific psychiatric disorder.

The affective disorders lend themselves well to an epidemiological approach. Because of the high prevalence of affective disorders, community studies are a feasible method of determining rates and risk factors; moreover, studies of persons in the community, not just in treatment facilities, are essential in order to understand the magnitude of the problem, because a large portion of depressives are never diagnosed or treated.

Several risk factors for some of the affective disorders have been reasonably well established through clinical case-control studies, such as the relationship between recent life events and the onset of depression; therefore, there is a preliminary understanding of what factors might be examined in epidemiological studies. Many potentially important risk factors, particularly biological ones, have not yet been incorporated into community studies.

Understanding the epidemiology of affective disorders has important implications for preventive intervention because a range of treatments is available, the efficacy of which has been established through well-designed clinical trials. There are opportunities for secondary prevention through early detection and treatment; moreover, before illness occurs, identification of risk situations, such as divorce or marital separation, or of high-risk persons, such as children whose parents are both depressed, could potentially have implications for primary prevention.

This section reviews the current understanding of the rates and risk factors for bipolar disorder and nonbipolar major depression.

DEFINITIONS

DIAGNOSTIC SCHEME Because an examination of the data from many studies reveals a number of diagnostic differences both internationally and over time, it is necessary to make assumptions about the comparability of the different diagnostic schemes.

The authors' review of the literature led to the conclusion that there is reasonable international agreement that bipolar disorder, defined by one or more episodes of mania, is a distinct diagnostic entity. The second group of depressives is a large and heterogeneous one that is comprised of persons with the depressive syndrome but without evidence or history of mania; these persons the authors call nonbipolar depressives. There is considerable international disagreement about how to define or subdivide this latter group. For example, in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, (DSM-III), the diagnostic classification for this group is major depression, which is further divided as to recurrence or symptom profile (melancholia). The ninth revision of the *International Classification of Diseases of the World Health Organization* (ICD-9) classifies depression according to impairment of reality testing, subdivided into psychotic or neurotic features.

In order to compare the more recent U.S. data, based on the Research Diagnostic Criteria (RDC) and DSM-III, with both the earlier U.S. data, based on DSM-II, and the European data, based on ICD, the data on bipolar disorder have been separated out as much as possible, and the remaining persons have been considered as an aggregate called nonbipolar major depression. The authors have ignored the heterogeneity of nonbipolar depression, as well as the debates on how to subdivide it.

This section will not address the epidemiology of depressive symptoms independent of diagnosis, because symptoms independent of diagnosis are not part of the DSM-III. Moreover, persons with depressive symptoms are a heterogeneous group, including persons with no psychiatric disorder, with psychiatric disorders other than affective disorders, as well as persons with physical illness whose symptoms overlap with depression. Therefore, it is quite difficult to interpret the epidemiology of depressive symptoms.

EPIDEMIOLOGICAL MEASURES AND APPROACH It is useful to define the different measures of risk that will be described when presenting rates. *Point prevalence* is that proportion of the population that has the disorder being studied at a given point in time. *Incidence* is the rate at which new cases of a disorder occur in the population at risk. *Period prevalence* is the proportion of the population that either has the disorder at the beginning of a specified time interval or has the disorder develop over the interval; thus, period prevalence is a hybrid measure that does not distinguish between incident and prevalent cases.

Lifetime risk for a particular psychiatric disorder is the proportion of a given population in whom that disorder would develop if all individuals lived to some specified age. As a way of estimating the lifetime risk of psychiatric disorders, some studies calculate the proportion of subjects in the general population who have had the disorder, i.e. *lifetime prevalence*. Other studies age-correct the denominator of this proportion by weighting unaffected persons by the proportion of the age of risk through which they have passed at the time that they ceased to be observed, i.e. *morbid risk* or *disease expectancy*. The major difficulty with morbid risk and disease expectancy, by this definition, is the ambiguity about the length of the risk period. As will be discussed, universal agreement has not been reached as to the age ranges during which persons are at risk to develop a major affective disorder for the first time.

The rates of affective disorders are usually based on community-wide studies of samples of a defined population, rather than solely on disordered persons coming for treatment; however, the risk factors have usually been identified from studies of depressed patients in treatment. The best studies are case-control studies in which depressed patients are compared with a matched control group of nonpatients with either another disorder or no disorder. In this way, it can be determined how the groups differ on the defined risk factors under study.

The risk factors selected for this discussion do not span the range of potentially useful areas for study. They have been selected because some data were available or because they are factors usually considered of interest in association with affec-

tive disorders. Notable by their absence are the biological measures, such as catechol-*o*-methyltransferase (COMT), methoxy,5-hydroxyphenylglycol, and neuroendocrine assays, that could be incorporated into epidemiological studies. This area is one of considerable interest and future direction in the next generation of epidemiological studies of affective disorders.

BIPOLAR DISORDER

DEFINITION The essential feature of bipolar disorder is a distinct period of elevated, expansive mood and associated symptoms of increased activity, pressure of speech, flight of ideas, inflated self-esteem, decreased need for sleep, distractibility, and excessive involvement in activities without recognition of the high potential for painful consequences. Because the majority of persons who experience manic episodes eventually develop depressive episodes, most investigators conceptualize unipolar manic episodes as being subsumed under bipolar disorder.

The old classification of "manic-depressive illness" is not synonymous with the DSM-III or the RDC classification of "bipolar disorder." There have been many epidemiological studies of manic-depressive illness, but the data rarely were broken down to show which patients had episodes of mania and which patients were unaffected. Kraepelin, who introduced the diagnosis of manic-depressive illness, argued that mania was not a different disorder from depression. Several studies of manic depressive patients have shown that most of the patients with this diagnosis have had episodes of depression without mania. It has been estimated that between 15 and 32 percent of hospitalized manic-depressive patients would meet the DSM-III criteria for bipolar disorder. Therefore, it is often difficult to calculate the rates of bipolar disorder from studies of manic-depressive illness.

RATES In 1981, a comprehensive review of the epidemiological literature found that the lifetime risk of bipolar disorder was less than 1.0 percent, ranging from 0.6 to 0.9 percent in industrialized nations. The annual incidence of this disorder, based on inpatient or outpatient treatment, ranged from 0.009 to 0.015 percent for men and from 0.007 to 0.030 percent for women. Because many persons with bipolar disorder are treated as outpatients and are never hospitalized, the first hospitalization rates for this disorder were somewhat lower and ranged from 0.003 to 0.008 percent for men and from 0.004 to 0.011 percent for women.

Since the 1981 review, the ECA results have become available, and the findings are consistent with the earlier review. The 6-month period prevalence for a manic episode ranges from 0.4 to 0.8 percent for men and from 0.4 to 0.9 percent for women. The lifetime risk of bipolar disorder in the ECA study was 0.9 to 1.1 percent for men and 0.6 to 1.3 percent for women, slightly higher than current rates. The rates were quite comparable across New Haven, Baltimore, and St. Louis, the three urban sites that were reporting data.

RISK FACTORS **Sex** In recent studies, the sex rates of bipolar disorder have been shown to be equal between the sexes. Earlier studies that use the diagnostic classification of manic depression show slightly higher rates in women, probably because most manic-depressive patients have had depression only, and depression is higher in women. When specified diagnostic criteria, such as DSM-III or RDC, are used to study bipolar disorder, the sex ratios are equal. The equal sex ratios for the disorder have been shown in recent family-genetic studies among first-degree relatives and also in epidemiological studies. The most convincing data come from the recent ECA study in which equal sex ratios for bipolar disorder were replicated in the same three urban sites mentioned above.

Age There is some disagreement between the earlier studies and the more recent ones on the age of risk for the onset of bipolar disorder. Recent studies suggest an early age of onset in late adolescence or the early twenties; the earlier studies found a rising incidence until age 35, then a decline. British studies have found that the incidence of mania increased with age, without any decline in the incidence rates; they also found that half of the new cases occurred in persons over the age of 50.

The age distribution of bipolar disorder is also affected by the pattern in the recurrence of episodes. Episodes recur every 2.7 to 9.0 years, and with increasing age, the interval between episodes becomes shorter, while the length of each episode increases. Consequently, persons with bipolar disorder will have an increasing risk of experiencing a manic or depressive episode as they grow older. Thus, while the age of onset may be young, the age of bipolar disorder patients in treatment may be older. In the ongoing Collaborative Study on the Psychobiology of Depression being conducted by the National Institute of Mental Health (NIMH), based on treated cases from six university centers throughout the United States, there has been a consistent finding of early age of onset—late twenties—for bipolar disorder, as compared with age of onset—late thirties—for major depression.

More recently, with improved case finding and with interest in applying systematic diagnoses to youth, there has been convincing evidence that, for some people, bipolar disorder begins in late adolescence. Some cases with onset in adolescence may be missed because of the notion that bipolar disorder does not occur in adolescence. Because the presentation may be mixed with antisocial disorder, temperamental patterns, or polydrug use, adolescents with early bipolar disorder may be diagnosed as having conduct disorder.

Social class Bipolar disorder may occur more frequently in the upper socioeconomic classes; however, it is unclear whether being from the upper social class is a cause or a consequence of bipolar disorder. There are three possible explanations: (1) A diagnostic bias may cause patients from lower socioeconomic classes to be inaccurately diagnosed; (2) a particular type of personality may dispose certain individuals both to the disorder and to a rise in the social scale; or (3) hypomania and cyclothymia may be an insidious onset of the disorder, but may lead to high achievement in school or at work. Bipolar patients have been shown to achieve higher levels of education and somewhat higher occupational status than a control group of patients with nonbipolar depression. Studies show that a high proportion of bipolar patients have been found among creative writers and among other professional men and women.

Early studies showed that the distribution of bipolar disorder and manic-depressive disorder was strikingly different from the distribution of schizophrenia. Areas of the city of Chicago marked by poverty and social disintegration showed a higher concentration of schizophrenia, but they did not show a similar concentration of affective disorders. More affluent areas of the city had slight concentrations of people with manic-depressive illness and bipolar disorder.

Race No relationship between race and bipolar disorder has been shown; however, no conclusions can be drawn as the data are scanty. Moreover, any study of the relationship

between race and bipolar disorder will need to control for social class.

Religion Bipolar disorder has been reported to be more common among Ashkenazi than among Sephardic Jews or non-Jewish groups. The disorder has also been found to be more prevalent among the Hutterites, a small inbred community of Anabaptists in the northwestern United States; however, the rates of bipolar disorder among the Amish, another small inbred community in Pennsylvania, are about the same as the rates for the general population. These "religious" groups may reflect genetic groupings, rather than the effect of religion as a belief system. Because of the ascertainment problems of small samples, the varying diagnostic methods, and confounding problems with social class, findings on the association of religious groups and bipolar disorder can only be considered suggestive.

Marital status Many studies suggest that bipolar disorder may be more common among divorced persons; however, marital status may be a consequence of the disorder, rather than a precipitant. A consistent finding is the relationship between bipolar disorder and marital disruption or conflict.

For example, earlier studies found a slight increase in the percentage of divorced people among persons with manic-depressive illness when compared with the general population, but found no greater frequency of being single, married, or widowed. In the Scandinavian literature, manic-depressive persons were less likely to be married than members of the general population and were more likely to be separated or divorced. In many cases, the illness preceded and probably contributed to the divorce. In the London area, the marital status and fertility of women with affective disorders, including bipolar disorder, were similar to the general population, as contrasted with schizophrenic persons, who have a lower likelihood of marriage or reproduction.

Rural-urban There are no published data on rural-urban differences in bipolar disorder. Limited data will be available from the ECA study because Durham, North Carolina—one of the six sites being surveyed—includes a rural population. In any study of rural-urban differences, social class must be taken into account.

Life events and social supports Although life events and social supports or personal resources have been actively studied for patients with nonbipolar depression, no specific data are available on those patients with bipolar depression.

Personality Most studies of personality in depressive patients either have not specified the diagnostic criteria or have not included bipolar patients as a separate group. One exception comes from the NIMH Collaborative Study on the Psychobiology of Depression. Recovered bipolar patients, as contrasted with nonbipolar depressive patients, had basically normal scores on measures of introversion and neuroticism when compared to established norms, and they differed only on measures of obsessionality.

Family history There is excellent evidence that bipolar illness is familial. Bipolar probands have an increase of both bipolar and unipolar first-degree relatives, and these rates are higher than might be expected in the general population or in control populations. The rates of bipolar disorder and cyclothymia are higher in the relatives of bipolar patients than in the relatives of nonbipolar depressed probands. Although the familial aggregation is a necessary condition for genetic transmission, it is not sufficient, because many familial characteristics are not genetic. The possible mode of genetic transmission, genetic linkage of subgroups of bipolars to human leukocyte antigen or to the color-blindness region of the X chromosome, and other biological markers of genetic vulnerability are areas of active research interest.

Thus far, the best evidence that familial aggregation may be reflecting genetic transmission comes from several twin studies where concordance for bipolar probands is greater than for unipolar monozygotic probands. A review of the genetics literature points out that one cannot reject the hypothesis that bipolar disorder is a more severe form of nonbipolar depression, with more genetic loading and greater penetrance than nonbipolar depression; however, more recent data are more equivocal.

In one study of 110 twin pairs, concordance for monozygotes was 0.67 and for dizygotes was 0.20. This datum was in close agreement with previous data from smaller studies. There has been only one adoption study dealing with bipolar adoptees. The bipolar adoptees had about a 3-fold increase of a broad spectrum of affective disorders in their biological parents, as compared with their adoptive parents or with the biological or the adoptive parents of the normal adoptees.

Consequences The consequences of bipolar disorder are serious and are important to note in any epidemiological review because they may be confused with risk factors for the disorder. The social and interpersonal consequences are the result of the explosive mood swings and poor judgments; they include marital instability, job loss, financial recklessness, alienation of family, alcohol abuse, and death by suicide.

NONBIPOLAR DEPRESSION

DEFINITION A "major depressive episode" is defined in DSM-III as a period lasting for at least 2 weeks that is marked by dysphoric mood and is accompanied by some of the following symptoms: a disorder of sleep and appetite, loss of energy, psychomotor agitation or retardation, loss of interest, self-reproach, difficulty in concentrating, and thoughts of death and suicide. Major depression differs from depressive symptoms in that the symptoms are persistent, impair functioning, and occur in the absence of other disorders that might explain the condition better. Most studies have presented data on various subclassifications of depression, such as endogenous, neurotic, reactive, involutional, psychogenic, psychotic, unipolar, the depressed type of manic-depressive illness, and depression not otherwise specified. As discussed previously in this section, all of these subclassifications of depression have been aggregated into one group called nonbipolar major depression. For example, if a study presented data on manic-depressive illness and also on psychogenic depression and psychotic depression, all the data were added together in order to arrive at a crude estimate of the rates of nonbipolar depression.

RATES The 1981 review of the epidemiological literature found the lifetime risk for nonbipolar major depression to be 8 to 12 percent for men and 20 to 26 percent for women. The annual incidence of nonbipolar depression, based on three longitudinal studies, varied more widely than any other rates, with ranges from 0.08 to 0.20 percent for men and from 0.25 to 7.80 percent for women. Due to the variable methods and the paucity of data, there was less confidence in these findings.

As a result of newer diagnostic techniques, more reliable data have become available on the prevalence of nonbipolar major depression. Table 18.2–1 shows prevalence figures from

TABLE 18.2–1
Prevalence of Major Depression (Based on Community Surveys of Noninstitutionalized Samples)

Study No.	*Place and Time*	*Diagnostic Criteria*	*Period of Prevalence*	*Men (%)*	*Women (%)*	*Total (%)*
1	U.S. National Survey	DSM-III	Annual	2.8	6.9	5.1
2	New Haven, CT* 1980–1981	DSM-III	6 mo	2.2	4.6	3.5
3	Baltimore, MD* 1981–1982	DSM-III	6 mo	1.8	4.1	3.0
4	St. Louis, MO* 1981–1982	DSM-III	6 mo	1.7	4.5	3.2
5	New Haven, CT 1975–1976	RDC	Current	3.2	5.2	4.3
6	Stirling County, Canada 1952	RDC	Current	—	—	4.1

* These figures are based on major depressive episodes and may include a sample number of subjects with previous episodes of mania.

six studies of probability samples of noninstitutionalized community samples. The diagnoses in these studies were based on the DSM-III or the RDC. The first study in Table 18.2–1 comes from a nationwide survey of psychotherapeutic drug use; a symptom checklist was used to derive DSM-III diagnoses. Studies 2 to 4 come from the ECA study; symptoms were obtained from the Diagnostic Interview Schedule (DIS), which computer-generated DSM-III diagnoses. Study 5 is based on the Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) interviews, which generated RDC diagnoses. Study 6 used a symptom checklist also, and in a reanalysis, RDC diagnoses were generated.

As can be seen, when similar sampling and diagnostic criteria are used, the results are remarkably similar. The current prevalence rates of major depression range from 1.7 to 3.2 percent for men and from 4.1 to 6.9 percent for women; the over-all current prevalence of major depression is between 3.0 and 5.1 percent.

RISK FACTORS **Sex** In almost all studies of depression in industrialized countries, roughly twice as many women as men are found to be depressed. The sex differences seem real and not an artifact of help-seeking behavior or reporting bias. Although women do seek treatment more readily than men, depressed women also predominate in community studies where help-seeking behavior is not a source of bias. The reasons for the sex differences in rates are unclear, but did suggest several areas of potentially fruitful exploration.

The 1½- to 2-fold increase in rates of major depression among women as compared to men was recently replicated in three ECA sites—St. Louis, New Haven, and Baltimore—in which more than 9,000 community subjects were studied. The higher rates of major depression (nonbipolar) are also found among the first-degree relatives of depressed and of normal probands in family-genetic studies.

A recent study of the Amish has been published citing equal sex ratios of major depression. This study is potentially important because alcoholism and sociopathy are virtually absent from this population. A presumed equal sex ratio could mean that alcoholism or antisocial behavior in males is obscuring male depression and that, when these behaviors in men can be eliminated, the sex ratios for depression become equal. The methodological problems of this study, however, such as biased ascertainment and diagnostic criteria that include an assessment of role impairment in work that may overrepresent the males who do heavy farm work, would preclude any conclusions from this study concerning sex.

Age A number of older studies were in agreement that the incidence and prevalence rates of depression in women reach a peak at the age of 35 to 45 years; however, recent epidemiological and clinical data suggest that the age of onset (incidence) of major depression occurs much younger. In the NIMH Collaborative Study on the Psychobiology of Depression the median age of onset seems to be the mid-twenties. Studies, including the ECA, are increasingly reporting high rates of major depression in younger populations. In part, this increase may be due to improved diagnostic techniques and systematic study, which have changed the older notion that depression did not occur in children or adolescents.

Historical changes A cohort effect, i.e. increasing rates of depression in populations born during the last 20 years, may be occurring. There is a convergence of findings from epidemiological, clinical, and family studies showing that the prevalence and incidence of depression seem to be increasing in younger-aged populations and seem to be decreasing in the older-aged population (ages 65 and older). These findings could represent a real change in rates or could be due to better ascertainment, the willingness of younger age groups to admit to depression, or the tendency for older subjects to deny or forget symptoms.

Menopause Neither the incidence nor the prevalence of nonbipolar depression shows a tendency to rise in the menopausal years. In fact, the rates tend to fall during those years. Recent research has suggested that menopause does not predispose to depression and that depression occurring in the menopausal period is not a distinct entity in terms of symptom patterns, severity, or absence of precipitants. Thus, eliminating involutional melancholia as a distinct diagnostic entity from DSM-III was in keeping with research findings.

Postpartum period Transient emotional disturbances in the first few weeks following delivery, the "new-baby blues," occur with such frequency as to be considered normal, and they generally resolve without treatment. There is overwhelming evidence, however, that the period up to 6 months postpartum also carries an excess risk for more serious psychiatric disorders.

Most authors agree that endocrine changes may be involved in postpartum psychiatric illness, although data linking hormonal changes to postpartum depression are lacking. In a previous era, many of the acute psychotic states that occurred postpartum, including delirium, were probably related to infections, fever, dehydration, and hemorrhage following childbirth. With better medical care, these symptoms are rare in industrialized countries, and today the severe postpartum psychiatric reactions are almost entirely of a depressive nature. It must be concluded that women are at greater risk for

psychiatric disorders, particularly depression, in the postpartum period; but if any specific endocrine abnormality is involved, the mechanism is not understood. Role changes, such as the responsibility of motherhood, and other psychosocial events of the postpartum period may contribute to the increased risk of depression.

Social class Whereas depressive symptoms and dysphoria independent of diagnosis are more common in the lower social classes, there is no particular pattern to the distribution of nonbipolar depression across various socioeconomic classes. This lack of association between the rates of nonbipolar depression and social class contrasts with the findings for bipolar disorder.

Race It has been widely documented that treatment for depression is less common among blacks than among whites; therefore, prevalence rates based solely on treated cases will underestimate the rates of depression among blacks. One study showed that, when hospitals became integrated in the United States, the rates of treatment for depression rose substantially among blacks. Community surveys thus far do not suggest a differential risk by race. One study in Uganda did show rates that were quite high among blacks; however, those rates may be due to Uganda being a developing nation. The epidemiological studies of depression across cultures have had too many methodological problems to warrant any conclusion; however, efforts to reconcile cross-cultural differences in diagnoses are under way through the World Health Organization.

Childhood experiences The relationship of early parental death to subsequent depression is controversial. There is evidence, however, that a disruptive, hostile, and generally negative environment in a child's home constitutes a risk factor for depression. Case-control studies have found such a home environment to exist more frequently in the backgrounds of depressed adults than in the backgrounds of the control group. The disruptive childhood home environment reported by adult depressives may be a reflection or a consequence of parental depression. Depressed parents have difficulty caring for their children, particularly in handling their own affects of anger and irritability.

Family history There is no question that depression is familial. A family history of depression doubles or triples the risk of depression. In several recent studies, the rate of major depression in the relatives of depressed probands was triple that of the relatives of normal probands, regardless of whether strict or loose criteria of depression were used in the relatives, and regardless of whether the proband was an ambulatory or hospitalized depressive.

Twin studies show that concordance for unipolar monozygotic twins is not as high as for bipolar ones, but is similar for dizygotic twins. Concordance is related to severity of illness. Major depressive patients with three or more episodes of depression show higher concordance than patients with few episodes.

Adoption studies dealing with unipolar disorder are rare. One study showed that the biological relatives of adopted persons with unipolar disorder had a higher rate of suicide than the biological or the adoptive relatives of control adoptees. Another small sample found an increase of depression (mostly unipolar) in the adoptees who had biological parents with affective disorders.

As with bipolar disorder, there is no question that family history is a strong risk factor for major depression. It is not yet clear whether this familial concentration of depression should be attributed to genetic, cultural, or environmental transmission of the disorder. The evidence for genetic transmission is less clear for nonbipolar depression than for bipolar disorder. At the present time, the type of interaction that takes place between genotype and environment in the etiology of nonbipolar depression is unknown.

Familial transmission of depression is complicated by "assortative mating," i.e. a tendency for a depressed person to have a spouse with depression. The risk of depression in an offspring is twice as high if both parents have depression than it is if only one parent has depression. There are several studies now investigating whether assortative mating results from people seeking someone with similar problems to marry or results from the depression of one spouse causing the other spouse to be at higher risk to become depressed after marriage.

Personality attributes Personality as a risk factor for depression has been a subject of considerable interest to clinicians and psychotherapists. A study of the personality profiles of 73 depressed patients with diagnoses based on RDC criteria, who were studied after recovery from their depression, suggested certain personality characteristics, such as likelihood to break down under stress, lack of energy, insecurity, introversion and sensitivity, tendency to worry, lack of social adroitness, unassertiveness, dependency, and obsessionality. The patients also showed higher introversion, neuroticism, guilt, and dependency scores when compared to the scores of both bipolar patients and the normal population. Such a profile is generally consistent with the literature from psychoanalytic, cognitive, and behavioral schools about the personality attributes of depressive patients. Future research in this area must separate the cause from the consequence of depression by studying persons prior to their first episode of the disorder. The experience of depression may alter personality, much as other chronic diseases have a debilitating effect, or the personality traits of such persons may be a manifestation of the same underlying genetic or situational etiology.

Recent life events In general, studies have shown that many, but not all, depressed patients, as compared with a normal control sample, tend to have an excess of negative life events, particularly losses or exits of significant others prior to the onset of a depressive episode. The precise magnitude of the effect of life events is unclear.

The best epidemiological approach to the study of life events was undertaken using life-event rates obtained in a case-control study (major depressive patients compared with a normal community sample). Ten percent of all exit events was followed by depression. Comparing the number of life events in depressed patients to matched controls, a relative risk of 6.5 for exit events in depression was obtained.

Absence of an intimate confiding relationship In a study of women in the Camberwell section of London, the absence of a satisfying intimate heterosexual relationship was shown to be a risk factor for depression. Because social factors predisposing women to depression included lack of an intimate tie or someone to trust and confide in, particularly a husband or boyfriend, a woman with these risk factors was 4 times as likely to break down in the presence of a severe life event. Lack of employment and the presence of young children in the home were additional risk factors for depression. It is not clear, however, whether these factors are specific for depression or for psychiatric disorders in general.

FUTURE DIRECTIONS

Accurate information on the prevalence, incidence, and risk factors for affective disorders from several ongoing studies is becoming available. In the United States, five large-scale epidemiological studies in New Haven, Connecticut; St. Louis, Missouri; Baltimore, Maryland; Durham, North Carolina; and Los Angeles, California have recently been initiated under the Epidemiologic Catchment Area (ECA) Program sponsored by the NIMH Division of Biometry and Epidemiology. These studies include interviews of probability samples of over 15,000 persons, including persons in institutions. Using a standardized research interview technique that generates DSM-III diagnoses, subjects are interviewed several times during a 1-year period. Thus, more defined information on the extent—both incidence and prevalence—of psychiatric disorders in the community will become available. So far, preliminary data from three sites are available and have been described.

In order to produce comparable data between different nations, it is necessary that similar methods of case definition be used. It is encouraging that the diagnostic instrument used in the ECA Program is being translated into other languages. In Shanghai, China, a study of several thousand persons has been conducted, and a similar study in Puerto Rico is under way. There is also a new collaborative effort under way between the Alcohol, Drug Abuse, and Mental Health Administration and the World Health Organization to sponsor a program on diagnosis and classification of mental disorders. Ultimately, a common mental health examination that is compatible with the European and the U.S. diagnostic systems, possibly based on the Diagnostic Interview Schedule and the Present State Exam, will be developed that will provide the basis for standardized generation of both DSM-III and ICD-9 diagnoses. Initial drafts of this instrument, called the Composite International Diagnostic Interview (CIDI), are being reviewed by an international group of experts. In addition, an important study sponsored by the World Health Organization on the diagnosis and course of treated depression in several countries is providing information on international diagnostic differences.

The variation in the prevalence and incidence rates of affective disorders can probably be diminished if a distinction can be made among the different subtypes of these disorders. At present, there is no international agreement about how to diagnose or subclassify nonbipolar major depression; however, the Collaborative Study on the Psychobiology of Depression being conducted at centers in Boston, New York, Chicago, St. Louis, and Iowa has as its main task the validation of diagnoses using descriptive, family, and follow-up studies as the criteria for validation. The preliminary data from these studies are beginning to yield promising information about the diversity of depressions, as well as information on both biological and psychosocial risk factors.

Once the problems of diagnostic standardization are sufficiently resolved, the next phase of epidemiological studies of the affective disorders will undoubtedly be directed toward the study of risk factors. Biological risk factors, measures of nutrition and infections, as well as a familial perspective, have been lacking in epidemiological surveys and will be areas of considerable attention in the next generation of epidemiological studies. Attention already is being given to the epidemiological assessment of psychiatric disorders in children and adolescents. With the apparent rising prevalence of affective disorders in younger persons, closer surveillance of the psychiatric status of younger populations is sorely needed.

SUGGESTED CROSS REFERENCES

A broader discussion of epidemiology appears in Section 6.1. The application of statistics to psychiatry is discussed in Chapter 7. The genetics of affective disorder is discussed in Section 18.4, and its clinical features are described in Section 18.5. Classification in psychiatry is discussed in Chapter 14.

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18.3 AFFECTIVE DISORDERS: BIOCHEMICAL ASPECTS

JOSEPH J. SCHILDKRAUT, M.D.
ALAN I. GREEN, M.D.
JOHN J. MOONEY, M.D.

INTRODUCTION

The biochemistry of depressive disorders has been an active area of scientific investigation since the introduction of the first clinically effective antidepressant drugs, imipramine and the monoamine oxidase inhibitors (MAOI's), in the late 1950s. In the 25 years since then, these first antidepressant drugs, as well as the newer ones as they have come along, have themselves become major research tools. Research into their mechanism of action has provided the basis for various working hypotheses about the biochemistry of depressions and has also led to more fundamental discoveries about the neurobiology of the central nervous system (CNS) itself.

The brain is known to contain billions of neurons, each one interacting with others by electrochemical means. When a neuron is stimulated, the resulting impulse, or electrical action potential, causes a release of a chemical substance

("neurotransmitter") from a specialized region in close proximity to a neighboring neuron. The neurotransmitter is released into a space between the two neurons called the "synaptic cleft." The neuron leading to the synaptic cleft is called the "presynaptic neuron"; the neuron leading away from the synaptic cleft is called the "postsynaptic neuron." The neurotransmitter released into the synaptic cleft from the presynaptic neuron briefly interacts with a receptor on the postsynaptic neuron, resulting in either electrical stimulation (increasing the likelihood of an action potential) or electrical inhibition (decreasing the likelihood of an action potential) of the postsynaptic neuron.

There seem to be many different substances that can act as neurotransmitters in the brain. There are also many other brain chemicals that can be regulators or modulators of this process. Pharmacological agents, such as the antidepressants, or environmental stimuli of many kinds ultimately exert their effects by altering this neurotransmitter-mediated interaction between neurons.

It may seem obvious that genetic factors may have biochemical expressions at the synapse; it must also be realized that environmental or psychological factors may act that way as well. Neurochemical and neurophysiological changes secondary to such factors can alter an individual's vulnerability to depressive episodes or even precipitate a depressive episode; therefore, sharp distinctions cannot be drawn between genetically and environmentally induced depressions or between biological and psychological depressions. Similar neurochemical or neurophysiological changes are probably involved to a greater or lesser degree in virtually every type.

This section will begin with a brief historical review of the neuropsychopharmacology of affective disorders. After this review, more detailed descriptions of selected aspects of recent research having some clinical relevance to the field will be discussed. The section will conclude with a brief overview of the emerging field of psychiatric chemistry.

HISTORICAL OVERVIEW OF NEUROPSYCHOPHARMACOLOGY The two major classes of antidepressant drugs, the MAOI's and the tricyclic antidepressants, were first used in psychiatry over 25 years ago. Within a few years after their introduction, several lines of evidence began to suggest that these medications worked at least in part through effects on catecholamines—one of many groups of chemical substances that function as neurotransmitters within the CNS. One of these catecholamines, norepinephrine, seemed to have particular importance in this regard. The first clue was that the MAOI's increased concentrations of norepinephrine in the brain by blocking one of norepinephrine's metabolic pathways. Shortly thereafter the drug imipramine, a tricyclic antidepressant, was found to enhance norepinephrine's effects by blocking a major inactivation mechanism; that is, the reuptake of norepinephrine into presynaptic neurons after release into the synaptic cleft. At about the same time, reserpine, a drug then used for hypertension, was noted both to deplete catecholamines in the brain and to cause clinical depressions in some patients.

On the basis of these and other data, the catecholamine hypothesis of affective disorders was formulated and introduced into the literature in the mid-1960s because of its potential heuristic value. This hypothesis, in its simplest form, proposed that some depressive disorders may be associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important synapses in the brain, whereas manias might be associated with an excess of such catecholamines. The emphasis on levels of catecholamines in the theory was based on the research techniques of the day that only allowed for measurement of the output and metabolism of norepinephrine released by presynaptic neurons. Nevertheless, the possibility of abnormalities in receptor function was also considered in formulating the hypothesis, because it was known that in the event of receptor subsensitivity a relative functional deficiency of norepinephrine could occur even with "normal" presynaptic output.

Because the broad clinical and biological heterogeneity of depressive disorders was recognized, it was apparent from the outset that this focus on catecholamine metabolism was, at best, an oversimplification of complex biological mechanisms. Alterations in many other neurotransmitter or neuromodulator systems were envisioned, as were ionic changes, endocrine changes, or other biochemical abnormalities. Nonetheless, the possibility that different subgroups of depressed patients might ultimately be characterized by differences in the metabolism of norepinephrine or in the physiology of noradrenergic (norepinephrine-containing) neuronal systems was an intriguing thought. Subsequent studies by many research groups have provided considerable data to support it. Other research in recent years has looked at other neurotransmitters or neuromodulators as well. In particular there have been studies on the relationship of the indolamine serotonin and acetylcholine to depression.

Over the last decade many investigations attempted to separate the depressive disorders into "noradrenergic" or "serotonergic" depression, depending on certain bicohemical data and particular responses to various tricyclic antidepressant drugs. This notion, based in part on presumed differences between various tricyclic antidepressant drugs in the inhibition of norepinephrine and serotonin reuptake, no longer seems tenable. Recent findings from studies of depressed patients, as well as recent data concerning the complex neuropharmacological effects of antidepressant drugs, make it obvious that such separations are overly simplistic and perhaps artificial.

The recent work with acetylcholine has suggested its role in the pathophysiology of at least certain types of depressive disorders. Drugs that stimulate acetylcholinergic activity have been found to induce depressions in control subjects, to exacerbate depressions in depressed patients, and to decrease manias in manic patients. Moreover, recent studies have suggested that some depressed patients may have supersensitive acetylcholinergic receptors that can be demonstrated not only during depressive episodes but also during periods of remission. It may be that anticholinergic effects of the commonly prescribed antidepressant drugs may be responsible for more than side effects; they may be of some importance in actual antidepressant effects of the drugs as well.

Neurotransmitters interact with specific receptors to exert their effects. Recent studies have shown that alterations in the biochemical and physiological properties of these receptors may be involved both in the mechanisms of action of antidepressant drugs and in the pathophysiology of depressive disorders. These possibilities are currently under active investigation in a number of laboratories throughout the world.

Moreover, it is becoming increasingly clear that the pathophysiology of depressive disorders is not restricted to abnormalities in brain function. Rather, the depressive disorders must be conceptualized as complex neuroendocrinometabolic disorders that involve many different organ systems throughout the body. The close connection to the endocrine system is just beginning to be examined. It seems obvious that in such an atmosphere many specialized laboratory tests, which are now starting to be used in psychiatry, will come to play an increasingly important role in the diagnostic evaluation and treatment of patients with depressive disorders.

BIOGENIC AMINES

NOREPINEPHRINE METABOLISM AND PHYSIOLOGY IN DEPRESSIVE DISORDERS The neuronal systems utilizing both norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5HT) originate as relatively small collections of cell groups located mainly in the brain stem. From there, the cell groups project widely into other brain centers. Such widespread projection makes these neuronal systems logical targets for psychiatric research; small changes in them can have widespread behavioral effects.

The noradrenergic cell bodies containing norepinephrine are found in the locus coeruleus, medulla oblongata, and pons. They distribute projections by two major pathways to the entire neocortex, limbic structures, thalamus, hypothalamus, reticular formation, dorsal raphe nucleus, cerebellum, sensory and motor brain stem nuclei, and spinal cord. Individual locus coeruleus neurons can simultaneously send collateral branches to the neocortex, hippocampus, cerebellum, and spinal cord. The norepinephrine projections from the locus coeruleus also regulate brain blood flow and capillary permeability.

One method of studying the activity of noradrenergic neurons in the brain is to measure the level of 3-methoxy-4-hydroxyphenylglycol (MHPG) in the urine. Known to be a major metabolite of norepinephrine originating in the brain, MHPG may also derive in part from the peripheral sympathetic nervous system. The fraction of urinary MHPG deriv-

ing from brain NE is uncertain. Despite this uncertainty, measurement of urinary MHPG has been used in attempts to elucidate the pathophysiology of depressions and to discriminate among biologically distinct subgroups of depressive disorders.

In longitudinal studies of patients with naturally occurring or amphetamine-induced bipolar manic-depressive episodes, many investigators have found that levels of urinary MHPG were low during periods of depression and high during periods of mania or hypomania. Comparably low MHPG values, however, do not occur in all types of depressions. This has raised the possibility that MHPG, or other catecholamine metabolites, may provide a biochemical basis for differentiating among subgroups of depressive disorders.

In early studies, urinary MHPG levels were found to be significantly lower in patients with bipolar depressions than in patients with unipolar nonendogenous chronic characterological depressions. Subsequent studies have confirmed the presence of reduced urinary MHPG levels in patients with bipolar manic-depressive depressions when compared to mean values in various subtypes of unipolar depressions or in nondepressed control subjects. One study suggested that the differences in urinary MHPG levels in bipolar manic-depressive depressions and control subjects became more pronounced when the peripheral contribution to urinary MHPG was reduced with carbidopa, a decarboxylase inhibitor that does not cross the blood-brain barrier.

In contrast to the reduction in urinary MHPG levels in patients with bipolar manic-depressive depressions, as compared with unipolar depressions, a number of studies reported no differences in urinary 3-methoxy-4-hydroxymandelic acid (VMA) levels. This is of importance because recent studies reporting that circulating MHPG may be converted to VMA have raised questions concerning the specific value of urinary MHPG (for example, in contrast to VMA) as an index of norepinephrine metabolism in the brain or as a biochemical marker in studies of depressed patients.

Patients with unipolar depressions have been reported to have a wide range of urinary MHPG levels: Low, intermediate, or high values have been found. It has been suggested that such a wide range may be due to diagnostic heterogeneity among the group of unipolar depressions. The low values are comparable to those seen in the bipolar depressions described above; the high values are sometimes above the normal range. Because normal values of urinary MHPG also tend to exhibit a broad range, urinary MHPG levels cannot be used to make a diagnosis of depression per se; yet, urinary MHPG levels may help in the differentiation of depressive subgroups.

Recent studies have described a subgroup of patients with very severe unipolar depressions whose urinary MHPG and urinary free cortisol (UFC) levels were both very high. It has been suggested that in this subgroup of severely depressed patients, increased acetylcholinergic activity may be a primary factor in the depression with elevated urinary MHPG and UFC as a secondary response. This suggestion is particularly intriguing when certain other recent data are considered: (1) physostigmine, an anticholinesterase, and other pharmacological agents that increase brain cholinergic activity exacerbate depressive symptoms in normal controls; (2) physostigmine produces an increase in plasma cortisol levels in normal controls; (3) physostigmine can overcome suppression of the hypothalamic-pituitary-adrenocortical axis by dexamethasone in normal subjects, thereby mimicking the abnormal escape from dexamethasone suppression seen in some patients who show cortisol hypersecretion (as described below); and (4) physostigmine produces an increase in cerebrospinal fluid levels of MPHG in normal subjects. This suggestion, thus, raises the unorthodox possibility that the anticholinergic effects of some antidepressant drugs, commonly regarded as side effects, may actually contribute to their antidepressant action in these patients with this depressive subtype.

In summary, there may be at least three distinct subtypes of depressive disorders that can be distinguished by urinary MHPG levels. Subtype I, with low pretreatment urinary MHPG levels, may have low norepinephrine output as the result of a decrease in norepinephrine synthesis or its release from noradrenergic neurons. (Many patients included in this subtype may be patients with underlying bipolar affective disorders who have not yet had their first episode of mania or hypomania.) In contrast, subtype II, with intermediate urinary MHPG levels, may have normal norepinephrine output but abnormalities in other biochemical systems. Subtype III, with high urinary MHPG levels, may have high norepinephrine output in response to alterations in noradrenergic receptors or to an increase in cholinergic activity, as described above. Further research is required to confirm these findings and to explore physiological abnormalities that may be associated with these subtypes of unipolar depressive disorders.

Although MHPG was the only catecholamine metabolite that was of value by itself for differentiating among subtypes of depressions, multivariate discriminant function analysis was used to explore the possibility that levels of norepinephrine (NE), normetanephrine (NMN), metanephrine (MN), and VMA might provide further useful data. This analysis led to the development of an empirically derived equation, termed the "D-type (Depression type) equation," that provided an even more precise discrimination between bipolar manic-depressive and unipolar nonendogenous chronic characterological depressions than did urinary MHPG alone. This discrimination equation is as follows:

$$\text{D-type score} = C_1\,(\text{MHPG}) - C_2\,(\text{VMA}) + C_3\,(\text{NE}) - C_4\,\frac{(\text{NMN} + \text{MN})}{\text{VMA}} + C_0$$

Subsequent as yet preliminary research using this equation has suggested that low D-type scores in patients with so-called "unipolar" depressions might aid in the identification of those patients having latent bipolar disorders even before the first clinical episode of mania or hypomania.

URINARY MHPG LEVELS AS PREDICTORS OF DIFFERENTIAL RESPONSES TO ANTIDEPRESSANT DRUGS

Studies from a number of laboratories have indicated that pretreatment levels of urinary MHPG may aid in predicting responses to certain tricyclic and tetracyclic antidepressant drugs. Depressed patients with "low" pretreatment urinary MHPG levels have been found to respond more favorably to treatment with imipramine, desipramine, nortriptyline, or maprotiline than patients with "high" MHPG levels. In contrast, some but not all studies have found that depressed patients with "high" pretreatment levels of urinary MHPG respond more favorably to treatment with amitriptyline than do patients with lower MHPG levels. Further research will clearly be required.

Urinary MHPG values trichotomized into the three subtypes described above may also be useful in predicting treatment responses. In preliminary data it seems that although depressed patients with elevated MHPG levels may be more responsive to treatment with imipramine or maprotiline than patients with intermediate levels, neither group is as responsive as patients with low MHPG levels. Moreover, patients

with low pretreatment urinary MHPG levels were found to respond rapidly to relatively low doses of maprotiline, whereas those patients with elevated MHPG levels (who responded to maprotiline at all) required significantly higher doses and longer periods of drug administration. This suggests a differential response or that the antidepressant drug, maprotiline, may exert different pharmacological properties in high doses than in low doses. This notion of relative sensitivity of different subtypes of depressions to antidepressant drugs may be analogous to the concept of relative sensitivity of different infectious diseases to antibiotic drugs.

Because administration of antidepressant drugs is known to produce multiple, complex effects on many neurotransmitter systems, empirical clinical trials may be required for the assessment of urinary MHPG levels, or any other biochemical measures, as clinically useful predictors of responses to a specific antidepressant drug. For example, preliminary reports from a recent placebo-controlled, multicenter collaborative study revealed the unexpected finding that patients with intermediate urinary MHPG levels responded more favorably to treatment with oxaprotiline than did patients with low or elevated MHPG levels. In contrast, the placebo response was similar in each of the three subgroups.

STUDIES OF RECEPTORS IN DEPRESSED PATIENTS Many investigators have suggested that alterations in receptor sensitivity may play a role both in the mechanism of action of antidepressant drugs, as well as in the pathophysiology of the depressive disorders. It may be that various subtypes of depressive disorders may be distinguished by particular receptor characteristics. The time course of the clinical effects of antidepressants has been linked to changes in receptor functioning.

Various pharmacological challenges of the CNS have been used in an attempt to clarify receptor properties, as well as the relationships between various neurotransmitter and neuromodulator systems. Endocrine responses have been actively examined in this regard. One endocrine finding that has been linked to a receptor change is the growth-hormone (GH) response to the α-adrenergic agonist, clonidine. In some depressed patients, the GH response is blunted; this has suggested a decreased sensitivity of postsynaptic α-adrenergic receptors in these patients.

Study of adrenergic receptors on human blood cells allows for an *in vitro* look at adrenergic receptors from psychiatric patients. Of course, these receptors may not reflect similar changes in the CNS; yet, they do provide a valuable research tool. For example, one group of investigators has reported the specific binding of the β-adrenergic antagonist ^{3}H-dihydroalprenolol to lymphocytes to be decreased in depressed and manic patients as compared to control subjects or euthymic patients. In addition, β-adrenergic receptor mediated stimulation of cyclic adenosine monophosphate (cAMP) production by isoproteronol was reduced in leukocytes and lymphocytes from depressed patients. More research is needed to clarify the significance of these findings suggesting decreased β-adrenergic receptor function in lymphocytes from depressed patients.

Studies of platelet α_2-adrenergic receptors, which suppress the activity of prostaglandin-stimulated adenylate cyclase, have also been reported on depressed subjects. In some studies, platelet adenylate cyclase (whether basal, prostaglandin-stimulated, or α-adrenergic suppression of prostaglandin-stimulated) has been reported unchanged. Nevertheless, a recent study of patients with unipolar depressions has reported that both prostaglandin-stimulated and α-adrenergic suppression of prostaglandin-stimulated adenylate cyclase were decreased. The discrepancies between these findings may reflect differences in platelet adenylate cyclase activity in subgroups of depressed patients.

Two studies have reported that the density of platelet high affinity α_2-adrenergic receptors (for α-adrenergic agonists) was increased in depressed patients. Moreover, these studies also showed that the total number of α-adrenergic receptors (high and low affinity), as reflected by α-adrenergic antagonist (^{3}H-yohimbine) binding, was unchanged. These findings, together with the finding of reduced α-adrenergic suppression and reduced prostaglandin stimulation of adenylate cyclase, may reflect a deficiency in the coupling between the platelet α_2-adrenergic (or prostaglandin) receptors and platelet adenylate cyclase in some unipolar depressed patients. This deficiency may involve the guanine nucleotide proteins that link hormone receptors to the catalytic unit of adenylate cyclase.

SEROTONIN METABOLISM AND PHYSIOLOGY IN DEPRESSIVE DISORDERS The cell bodies of serotonergic neurons are located in the raphe nuclei and superior central nucleus; their axons project widely throughout the CNS—to the entire neocortex, entorhinal cortex, thalamus, hypothalamus, limbic structures, reticular formation, locus coeruleus, cerebellum, and spinal cord. As is true of noradrenergic neurons, such a widespread projection of serotonergic neurons makes them logical candidates for psychiatric research. In many regions the serotonergic and noradrenergic projections overlap with each other; there is at least one major interface between the raphe nuclei of the serotonergic system and the locus coeruleus of the noradrenergic system.

A number of lines of evidence suggest that some patients with depressive disorders may have abnormalities in serotonin metabolism and physiology. A number of studies have found that some depressed patients have reduced levels of 5-hydroxyindoleacetic acid (5HIAA), a metabolite of serotonin, in the spinal fluid. Some other studies have noted an association between increased incidence of completed suicide, suicidal attempts, or acts of aggression with a reduced level of cerebrospinal fluid 5HIAA.

In several older studies the brains of suicide victims were found to have low concentrations of serotonin. More recent research, looking at the brains of suicide victims, has found that the binding of ^{3}H-imipramine, which is thought to bind to serotonergic nerve terminals, was decreased, whereas there were increases in the numbers of postsynaptic serotonin ($5HT_2$) receptors. Such research findings have led a number of investigators to suggest that there may be a serotonergic deficiency in suicide victims or in those depressed patients who attempt suicide.

Decreased serotonin uptake into platelets has been observed in patients with depressive disorders. ^{3}H-imipramine binds to brain and platelet high affinity sites that are thought to be near the cellular uptake regulation sites for serotonin. A highly significant decrease in the number of binding sites with no significant change in the apparent affinity constant has been observed in platelets from depressed patients compared with those from control subjects. It has been proposed that decreased platelet ^{3}H-imipramine binding observed in depressed patients may reflect a deficiency in the platelet serotonin transport mechanism in these patients.

PLATELET MAO ACTIVITY IN DEPRESSIVE DISORDERS In the early 1970s, platelet monoamine oxidase (MAO) activity was reported to be increased in a heterogenous group of depressed patients (most of whom had unipolar depressions) and decreased in a group of bipolar depressed patients. Subsequent results have not been as clear. For example, some

investigators have recently reported increased platelet MAO activity in patients with unipolar endogenous depressions; others have reported increased platelet MAO activity in patients with unipolar nonendogenous depressions. Because each study used different criteria for the diagnosis of endogenous or nonendogenous depressions, as well as different methods to determine platelet MAO activity, it is not possible to clarify these conflicting data at the present time.

Several studies have recently reported the unexpected association between increased platelet MAO activity and increased activity of the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients. Elucidation of the clinical and pathophysiological significance of this intriguing association may help to clarify aspects of the confusing and seemingly contradictory literature on platelet MAO activity in relation to subtypes of depressive disorders.

In some recent studies, platelet MAO activity was found to correlate both with the severity of the depression, as well as with anxiety symptoms and somatic complaints. The clinical items found to be correlated with platelet MAO activity in these studies corresponded to symptoms reported by other investigators to be associated with favorable responses to treatment with MAO inhibitors. Other studies have found an association of high platelet MAO activity with social introversion or asociality and of low platelet MAO activity with social extroversion or sensation-seeking.

Additional studies will be needed to determine whether such clinical (psychometric) variables may help to account for the differences in platelet MAO activity that have been observed in various subgroups of depressions. Furthermore, research will also be required to compare kinetic parameters (and other properties) of platelet mitochondrial MAO with other biological indicators in patients with various subtypes of depressive disorders, and in control subjects as well.

PSYCHONEUROENDOCRINOLOGY

The possibility that hormones might somehow be related to affective states has long been considered. A logical link was established with the earliest clinical descriptions of Cushing's disease and hypothyroidism, both of which are associated with changes in mood. The exact relationship between the endocrine system and the brain as mediator of behavior, however, was unclear for years. In fact it was not until the late 1940s that the neurovascular model linking the hypothalamus and the pituitary was first proposed, and it was not until the mid-1950s that the existence of a substance in pituitary extract that stimulated the release of adrenocorticotropic hormone (ACTH) was demonstrated. This substance was called corticotropin-releasing factor (CRF), but its structure eluded investigators until quite recently. In about the last decade, a number of hypothalamic peptides controlling the anterior pituitary gradually have been isolated and synthesized: thyrotropin-releasing hormone (TRH), gonadotropin releasing hormone (GnRH), growth hormone releasing inhibiting factor (GHIF or somatostatin), growth hormone releasing factor (GHRF), and most recently, CRF itself. This delineation of the intricate hypophysiotropic system and the recent development of sensitive hormonal assays have allowed for an explosion in research on endocrine systems and psychiatry.

The activity of the limbic system—long suggested to be the CNS site of affective states—is regulated by many of the neurotransmitters thought to be involved in the pathophysiology and, possibly, the etiology of affective states. The limbic system in turn regulates pituitary hormone release, a key element in the endocrine network. Thus, many investigators have examined endocrine changes in affective illness in an attempt to obtain information concerning possible functional alterations of certain CNS neuronal systems that use one or another neurotransmitter or neuromodulator. This strategy has been likened to looking at the brain through a "neuroendocrine window." Another strategy in recent psychiatric studies has been more practical. This has involved the search for one or more laboratory tests of endocrine function that might distinguish certain affective subtypes from other subtypes or affective illnesses from other psychiatric illnesses.

The neuroendocrine network is a highly complex, well-integrated system. It involves the release of anterior pituitary hormones by various hypothalamic factors, a feedback control onto this release from circulatory target organ hormones, and an overriding control on the entire system by internal biological rhythms or external events impacting on the hypothalamus.

The methods used for studying the endocrine network as it relates to affective disorders are multifaceted. First, because each bodily hormone is released according to a circadian rhythm, the study of possible changes in the rhythm in an affective disease state is of interest. Second, the response of the anterior pituitary to the introduction of a hypothalamic factor (principally TRH and GnRH, and recently CRF) can also be measured in affected patients and compared with normals. Third, direct challenges to the hypothalamus itself, such as insulin-induced hypoglycemia, provide further information about the functioning of the axis. Fourth and finally, provocative neuropharmacological challenges with such drugs as amphetamines, clonidine, or physostigmine can also be used to test for changes in neurotransmitter systems in affective disease states.

Hundreds of studies using one or another of these strategies have resulted in an enormous volume of information in just the past decade. The studies are often conflicting, yet one conclusion seems sure: Various endocrine changes are associated with affective disorders. Best documented are changes involving the hypothalamic-pituitary-adrenal (HPA), the hypothalamic-pituitary-thyroid (HPT), and the hypothalamic-pituitary-growth hormone (HPGH) axes.

The material under the next five headings will detail particular disturbances. Most of the work has involved patients with unipolar depressions, but studies on bipolar patients will be noted where applicable. Because the field is changing rapidly, and every month brings a spate of new articles on one or more of the endocrine changes, the material below can best be used as a background guide to the status of the field in mid-1983.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS The HPA axis has been extensively studied in affective disorders. CRF, a hypothalamic peptide recently identified, stimulates the release of ACTH from the anterior pituitary. ACTH causes the adrenal cortex to secrete cortisol that, in turn, regulates the further release of CRF from the hypothalamus. The entire HPA system has a circadian rhythm; most of the cortisol released from the adrenal glands comes in periodic bursts in the early morning hours. The regulation of CRF is complex and involves various neurotransmitters and neuromodulators, including acetylcholine, serotonin, and norepinephrine.

Hyperactivity of the HPA axis in depressed patients has been extensively reported over the past decade. Cortisol hypersecretion, documented by 24-hour urinary free cortisol output or cortisol production rates, has been found in approximately one-half of the depressed patients studied. These cortisol hypersecreters show a characteristic flattening of their circadian cycle, such that they secrete cortisol during the time

of day when such secretion is normally at a minimum. The cortisol abnormality seems related to the depression per se, is not merely due to stress or hyperactivity, and typically reverts to normal with clinical remission.

The dexamethasone suppression test (DST) has been used extensively to study the HPA axis in patients with affective disorders. First introduced in 1960 for the study of Cushing's disease, this procedure determines whether administration of dexamethasone results in normal suppression of the HPA axis as determined by lowered concentrations of cortisol in blood at various times after the administration of dexamethasone. Two groups of investigators, working independently, began applying the DST to depressed patients in the late 1960s; both groups found abnormal DST values (failure of dexamethasone to suppress cortisol secretion) in some of the patients with endogenous depressions. A number of seminal reports in the early 1980s led to widespread interest in the use of the DST in psychiatric research and practice. These reports specified (1) an optimal method (1 mg of oral dexamethasone with 4-P.M. and 11-P.M. plasma cortisol measurements); (2) sensitivity (67 percent); (3) specificity (96 percent, if strict exclusion criteria are followed); and (4) a cut-off for normal postdexamethasone plasma cortisol (5 μg/dL).

Recent literature contains many reports both confirming and questioning various aspects of the early DST findings. The reported sensitivity level has been confirmed by many other investigators for patients variously described as having major depressive disorder, primary depression, or endogenous depression. The percentage of positive (abnormal) tests in patients with unipolar psychotic depressions has been found to be higher than in nonpsychotic melancholic patients; the actual cortisol concentration in 4-P.M. postdexamethasone blood samples may be significantly higher in these patients as well. The percentage of abnormal DST's is often reported to be lower than 50 percent in outpatients, perhaps either because of the use of only one cortisol sample at 4 P.M. or because outpatients may be more heterogeneous and, as a group, have less "severe" depressions. The association of abnormal DST results with a family history of depression has been reported by some investigators but not by others. Some investigators, moreover, have suggested that the DST abnormality cuts across many different diagnostic categories and may define a diagnostically broader, but biologically more homogenous, group of disorders than melancholia per se.

The DST abnormality appears to be stable over the course of a depressive episode and to remit with clinical recovery. Subsequent depressions in a particular patient seem to run true; suppressors in one depression tend to be suppressors in the next. The change in the DST with treatment precedes the clinical recovery; some have suggested that an incomplete normalization of the DST, irrespective of the clinical symptomatology, indicates an incomplete resolution of the depressive process. Others have advocated serial use of the DST to determine the safe period for withdrawing antidepressant medication because a number of studies report that incomplete normalization of the DST predicts high likelihood of relapse. After electroconvulsive therapy (ECT), however, the picture does not appear to be clear; the possibility has been raised that ECT itself may interfere, at least temporarily, with the DST.

There has been much discussion of whether an abnormal DST predicts treatment response. Most, but not all, studies have suggested that patients with abnormal DST's before treatment exhibit a greater degree of improvement with antidepressant treatment than those with normal DST's. An interesting and currently unresolved debate in the literature has begun over the question of preferential response to certain antidepressants.

The issue of the specificity of the DST for depression is an important one; in large measure it determines the clinical utility of the test. With the multiple conflicting reports in the literature, the issue in mid-1983 remains unresolved. The rate of false-positive results on the DST in normal subjects, which has varied from 4 percent to over 10 percent in different reports, represents one facet of the specificity question. Two other issues are: What conditions will interfere with the test, and what psychiatric states other than depression may produce false positive results. Not taking the dexamethasone will interfere; the patient will then have a normal diurnal cortisol fluctuation that will be interpreted as an abnormal DST. Even if compliance is assured, however, a number of medical disorders and pharmacological agents can produce false-positive or false-negative results. In addition, weight loss per se, often an accompaniment of major depressions, may cause an abnormal DST result.

The literature on psychiatric conditions other than depressions that may be associated with an abnormal DST is, at this writing, somewhat confusing. The DST does not appear to be generally abnormal in panic disorder or borderline personality disorder, two conditions linked with depression. An abnormal DST, however, is observed in many patients with depression-like states after strokes and also in withdrawing alcoholics. Although a number of investigators have found normal results on the DST in schizophrenic and manic patients, the recent literature contains a few reports of a significant percentage of abnormalities on the DST in both diagnostic groups.

As might be expected from the conflicting published reports, the possible clinical utility of the DST has attracted considerable controversy. Some investigators have suggested that it may be useful either in patients for whom the diagnosis of depression is not obvious or as a method for monitoring successful treatment. Others have suggested that the DST has little clinical value. The discussion rages on in print and at meetings. A number of recent studies agree that the DST may have particular value in the diagnosis of prepubertal and adolescent children in whom the clinical symptomatology of depression may be atypical and the DST may be abnormal. At the other end of the age spectrum, the question of the DST in depressive pseudodementia is muddled. The test itself does not appear to become abnormal with age alone, but a large percentage of nondepressed demented patients have been reported to have abnormal DST values.

It seems safe to say that the DST is a reproducible test that detects some abnormality in the HPA system in certain depressed patients. Although it is an extremely valuable research tool, the question of what the underlying biological abnormality picked up by the DST may be remains to be answered by future research. Recent findings of an association with shortened rapid eye movement (REM) latency and increased MHPG in some depressions have led to speculation about a possible adrenergic/cholinergic imbalance. Further data about the effects of physostigmine and amphetamines on the DST or cortisol levels have given more substance to this possibility.

The recent finding of an association of abnormal HPA activity with elevated platelet MAO activity in depressed patients remains to be elucidated. Further clarification of the HPA abnormality and its relationship to other biological variables must also be pursued. As a result of such research, the next edition of this textbook may be better able to delineate the specific HPA defect in depressive disorders, its underlying biological substrate, and the optimal clinical utility of whatever tests most reliably detect it.

HYPOTHALAMIC-PITUITARY-THYROID AXIS The HPT axis has received almost as much attention as the HPA axis. Interest in the thyroid and its function in emotion dates back centuries. Modern investigation can be traced to a 1938 report that suggested that some patients with periodic catatonia improved when they received thyroid extract. Approximately 40 years later it was suggested that small doses of triiodothyronine (T3) potentiated the antidepressant effects of tricyclics in women. More recently, it was shown that the thyrotropin (thyroid-stimulating hormone, TSH) response to thyrotropin-releasing hormone (TRH) was decreased in some depressed patients.

TRH is a tripeptide that stimulates the release of TSH, prolactin, and, in some instances, growth hormone from the anterior pituitary. Early reports suggested that when TRH was given to depressed patients, they experienced a rapid although short-lasting improvement in their mood. Other investigators, however, were not able to confirm this finding, which at present seems to have little clinical utility in psychiatry.

The issue of a decreased response of TSH to TRH stimulation, however, is another matter. As with dexamethasone nonsuppression, the blunted TSH response to TRH has been confirmed by many investigators; and as with the DST, TRH stimulation is a useful research tool that may have clinical value as well. The TRH test, a measure of the change of TSH after administration of TRH, is a routine endocrinological procedure. In medicine it is used mainly for the evaluation of patients with dysfunction of the HPT axis, is often helpful in pinpointing the source of the dysfunction, and is considered to be a safe procedure. The usual side effects after administration of TRH are very brief and include feelings of nausea, an unpleasant taste, an urge to urinate, a light-headed sensation, and headache.

Results of this test have been reported in over 1,000 depressed patients in nearly 50 different studies over the past decade. There seems to be remarkable agreement that at least some of these depressed patients, with apparently normal thyroid status, have a blunted TSH response to TRH.

The test has been standardized and is generally performed as follows. After an overnight fast, the patient is placed in a recumbent position. An intravenous (IV) line is started in the morning, and a baseline TSH is drawn. The TRH is then injected IV, and multiple blood samples are taken at intervals over the next 90 minutes for TSH measurements. The test result is usually expressed as Δ_{max} TSH, or the highest TSH value after the TRH minus the TSH value before the TRH. Because in depression the TSH values are likely to be low, the laboratory assay (generally a radioimmunoassay) must be sensitive to these low levels. (Standard clinical laboratories may not be able to detect such small values without some modification of their assay.)

The data on the TSH response have been reported either as group means or as a percentage of blunting for individual patients. Studies using group means have clearly indicated that, as a cohort, depressed patients have a lower TSH response to TRH than normal persons. Reports on percentage of blunting vary from about 25 to 70 percent depending on the definition of blunting and the diagnostic groups studied. Some groups have found that those patients with a blunted TSH response also had a blunted prolactin response or an abnormal GH response, but other groups have not. The possibility of differences between bipolar and unipolar depressions in the blunting of the TSH response to TRH has been raised but not resolved in the literature.

A number of factors are known to cause blunting in normal persons. Most important for the use of this test in psychiatry are increasing age and being male. Many of the reported studies in depressed patients are hard to interpret because of lack of adequate controls. Other factors that may be related to blunting in normals include acute starvation, chronic renal failure, Klinefelter's syndrome, repeated TRH tests, and administration of somatostatin, neurotensin, dopamine, thyroid hormone, or glucocorticoids. Because of the effect of glucocorticoids on the TRH test, it was postulated that the blunted TRH test in depressives might be an epiphenomenon of an elevated plasma cortisol, known to be found in many depressed patients. A number of recent studies, however, have clearly separated these two factors into distinct subgroups and suggest that the TSH blunting is a discrete phenomenon unrelated to the HPA abnormality.

The possible diagnostic significance of the TSH blunting has been a subject of some debate. As noted above, a number of studies have suggested that about 25 to 70 percent of patients variously described as having endogenous, primary, or major depressions also have a blunted TSH response to TRH. In two separate studies, patients with the TSH blunting were not found to be within particular familial subtypes of depression. Only a few studies have specifically reported on the TSH response in neurotic or minor depressions; but, in those, the TSH was normal, as it was also in groups of patients with secondary depressions, schizophrenia, and acute paranoid reactions. Normal TSH responses, but with delayed time course, have been reported in anorexia nervosa. Alcoholics, both during and after withdrawal, have been reported to have TSH blunting in the range of 25 to 60 percent. Some patients with borderline personality disorder may have blunting as well.

It is obvious that the finding of a blunted TSH response to TRH is not specific for endogenous depression. Some have suggested, however, that with the proper exclusion criteria, it is useful in the differential diagnosis of dysphoric states. Others do not agree. This argument has not yet been resolved in the literature.

There is no disagreement that the TRH test has great potential utility for research. An important research question is that of normalization of the TSH blunting with clinical improvement. In some depressed patients, the TSH response seems to change with symptomatology. A number of studies, however, have found that not all of the blunted responses in depressed patients return to normal with clinical improvement. Similarly, TSH responses have been reported to be blunted in some alcoholics both during and long after withdrawal. It has been suggested, therefore, that the TSH response to TRH may have trait as well as state characteristics. This possibility, that the TSH blunting may be a partial trait marker, has stimulated recent studies of the nondepressed relatives of TSH-blunted depressed patients.

One group of investigators has reported on the prognostic value of the TRH test. They followed a cohort of clinically recovered depressed patients to determine relapse rates based on an index of change in the TRH test known as the $\Delta\Delta_{max}$ TSH, which is defined as the TRH test result (Δ_{max} TSH) after a favorable treatment response minus the result before treatment began. In their studies, a $\Delta\Delta$TSH of >2 μU/ml was associated with no relapse within 6 months 93 percent of the time, whereas a value of ≤ 2 μU/ml predicted a relapse within 6 months 89 percent of the time. In all the cases no maintenance treatment had continued after the clinical response. They suggest that the $\Delta\Delta$TSH might be helpful in determining when to stop treatment. Another investigator has confirmed the finding, but in his study even continued antidepressant

therapy did not prevent relapse in those patients with a $\Delta\Delta$TSH of ≤ 2 μU/ml.

A number of investigators have recently reported on the relationship of the TRH test blunting to other biological measurements in depressed patients, but clear-cut confirmed findings have not yet emerged. Studies such as these that combine multiple tests can be expected to become increasingly common in the coming years.

The pathophysiological significance of the TSH blunting in affective disorders is not clear. Hypersecretion of TRH could lead to down-regulation of the pituitary response; that is, TSH blunting. This possibility is supported by a report in the literature of elevated TRH in the cerebrospinal fluid of depressed patients.

As stated above, TSH blunting in depression is found in patients with normal thyroid functioning. Recent reports suggest that some depressed or rapid cycling patients, particularly women, may have subclinical hypothyroidism as detected by an elevated TSH or augmented TSH response to TRH. These patients may respond to thyroid hormones, which are known to potentiate antidepressant action. A possible mechanism may be a thyroid modulation of adrenergic receptors.

HYPOTHALAMIC-PITUITARY-GROWTH HORMONE AXIS The third endocrine system studied in patients with affective disorders is the hypothalamic-pituitary-growth hormone (HPGH) axis. Investigators have looked at levels of growth hormone and somatostatin (growth hormone releasing inhibitory factor) as well as the growth hormone response to various stimuli, such as insulin hypoglycemia, L-dopa, 5-hydroxytryptophan, apomorphine, *d*-amphetamine, clonidine, and TRH. The findings in patients with affective disorders have been, in general, confusing; the HPGH axis is a very complex one.

Growth hormone is elevated during stress and in relation to the first nightly cycle of slow-wave sleep, but GH also seems to be released in 6-hour intervals throughout each 24-hour day. Basal GH levels in depressed patients are reported to be normal, despite the apparent stress of the illness. Somatostatin, however, when measured in the CSF, has been reported by two separate groups of investigators to be diminished in depressed patients but normal in manic patients. The level reverts to normal with clinical improvement. There was some suggestion that the diminished somatostatin may be related to the altered sleep pattern seen in the patients.

As noted above, stimulation by L-dopa (L-dihydroxyphenylalanine) has been used as a measure of GH response. The reported data after the use of this stimulus, unfortunately, provide an excellent example of the confusing and changing information in the literature about GH in affective illness. An early report suggested that depressed patients had a lower GH response to L-dopa; however, in a subsequent study, when age, sex, and menopausal status were controlled, the diminished GH response to L-dopa disappeared.

Similarly, the use of amphetamine as a probe in patients with affective disorders has also produced data, the interpretation of which has changed over recent years. Its use is based on evidence that catecholamines may play a role in the CNS control of GH release. An early study reported that the GH release after IV amphetamine administration was lower in endogenous depressives and higher in reactive depressives as compared with normals. A subsequent report, however, suggested that age or estrogen status greatly influenced the amphetamine effect on GH. A restudy of GH release, with adequate control groups, did not confirm the original findings in depressed patients.

There has been in recent years an interesting series of reports about abnormal positive GH responses to TRH in depressed patients. As discussed above, TRH normally causes the release of TSH and prolactin only. According to three separate groups, GH increases are detected in approximately 50 percent of patients with either unipolar or bipolar depressions but in no patients with a minor depression. This abnormality ceases with clinical recovery; however, two other groups have found no growth hormone response to TRH in depressed patients. It is unclear at this time why such inconsistent findings are being reported. Further studies are required.

A number of investigators have noted a reduced GH response to an insulin stimulus in some depressed patients. It has been reported to be more severe in psychotic depression and, in some cases, to persist following clinical recovery. One report noted the GH reduction to be more pronounced in bipolar than in unipolar depressions, yet another report had just the opposite finding. A recent preliminary publication, however, which controlled for adequacy of hypoglycemic response to the insulin stimulus before measuring GH, found no evidence that the HPGH system is altered in depression.

The explanation for the conflicting results of GH after insulin may lie in the hypoglycemic response. Unipolar depressives have recently been shown to have an inadequate hypoglycemic response to insulin as compared with bipolars or normals. In addition, those unipolar patients with an inadequate response are more severely depressed than those with an adequate response. This is consistent with longstanding reports in the literature that glucose utilization is lowered in endogenous depressions. This decreased utilization is reflected in impaired glucose tolerance in some depressed patients (as measured by the glucose tolerance test) and in a blunted hypoglycemic response to insulin during the acute phase of depression.

The HPGH axis, as it relates to the pathophysiology of depression, requires further study. As mentioned under the earlier heading, "Studies of Receptors in Depressed Patients," the GH response to clonidine stimulation has been used as a test of the responsiveness of α-adrenergic receptors. At least four independent groups have recently demonstrated that the GH response to clonidine is blunted in some depressed patients; however, such an abnormality or any other abnormalities that may be shown to exist in this axis will be exceedingly difficult to interpret because of the complexity of the system.

HYPOTHALAMIC-PITUITARY-PROLACTIN AXIS Prolactin, an anterior pituitary hormone with multiple action throughout the body, has been examined in affective illness. At the present time, however, the existing data are confusing. It is not possible to predict whether measurement of prolactin will prove to be useful either as a clinical laboratory test or as a clue to underlying pathophysiology in subtypes of depressive disorders.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS The hypothalamic-pituitary-gonadal axis has not been as extensively examined in the affective disorders as have the other hormonal systems. Although the loss of libido in depressions has led to the common belief that sex hormones may play some role in the affective illnesses, the existing data are limited and difficult to interpret.

BEYOND THE CATECHOLAMINE HYPOTHESIS: TOWARD A BIOCHEMICAL CLASSIFICATION OF DEPRESSIVE DISORDERS

For the past 20 years, the catecholamine hypothesis of affec-

tive disorders has been of considerable heuristic value. When first described, this formulation provided investigators and clinicians with a frame of reference that integrated much of the prevailing knowledge and experience with the pharmacological agents that produced alterations in human affective states. Over the course of the following years, the catecholamine hypothesis helped to stimulate the growth and proliferation of research on many aspects of the biochemistry of depressive disorders.

At the present time the field seems to be in a new phase characterized by the broad-ranging accumulation of empirical data, much of which cannot be encompassed within any one theoretical framework. The new data, as reviewed above, make for a confusing and certainly incomplete picture. New information comes tumbling out of every new issue of a psychiatric journal. Much of what seems true or even defensible in mid-1983 may be found to be artifactual or even false by the time this edition of the *Comprehensive Textbook of Psychiatry* reaches publication. Nevertheless, two facts seem clear: The depressive disorders seem to be a group of interrelated neuroendocrinometabolic disorders, and biochemical procedures will be required to subdivide and classify these disorders.

THE EMERGING FIELD OF PSYCHIATRIC CHEMISTRY

It seems reasonable to predict that the field will continue to work toward the development of a biochemical classification of depressive disorders by using, in part, empirically derived clinical laboratory tests that document one or another aspect of the pathophysiology of these disorders. It seems highly unlikely, however, that a truly comprehensive understanding of the etiology and pathophysiology of the depressive disorders will exist until a parallel description of the functional neurochemistry and neurophysiology of the normal human brain becomes available. Kandel's pathfinding studies, using animal models to explore specific forms of mentation on the cellular and molecular levels, document the feasibility of such an undertaking; however, these studies also emphasize how far off is the attainment of this goal. Thus, in the foreseeable future, psychiatric practice may be guided by the use of specialized clinical tests that the theory of psychiatry may not meaningfully integrate for many years. In this regard, however, psychiatrists are in a position quite similar to that of their colleagues in other medical specialities.

Recognizing this fact, the Harvard Medical School Department of Psychiatry and Department of Pathology of the New England Deaconess Hospital established a Psychiatric Chemistry Laboratory in 1977 to serve as a model academic laboratory for the integration and translation of biochemical research into clinical psychiatric practice. In addition to providing specialized clinical laboratory tests for psychiatry, an explicit aim of the Psychiatric Chemistry Laboratory has been to provide physicians with educational and consultative services in the use and interpretation of these tests.

In conclusion it may be useful to draw an analogy between the pneumonias and the depressions. Both of these disorders are diagnosed on the basis of clinical data, and both of these disorders are best treated using information gleaned from clinical tests. In the case of pneumonias, the physician makes a diagnosis on the basis of history and physical examination (including a chest X-ray). Having made the diagnosis, sputum cultures can then be obtained to aid in determining the specific type of pneumonia that the patient may have and the specific antibiotic or other forms of treatment that may be most effective, irrespective of why the pneumonia developed. Similarly, in the case of depressions, the physician diagnoses depression on the basis of clinical history coupled with physical and mental status examination. Having made a diagnosis of depression, a physician can then use specialized clinical laboratory tests to obtain further information to assist in determining the type of depression the patient may have and the forms of treatment most likely to be effective in the care of that patient.

Although the biochemical tests available today do not necessarily enable physicians to select a clinically effective treatment on the first trial, the use of these clinical laboratory tests can increase the probability of their doing so. Considering the time it takes for antidepressant drugs to exert their clinical effects, even a small increase in the percentage of patients who receive an effective drug on the first clinical trial of treatment would represent a major advance in the treatment of patients with depressive disorders.

SUGGESTED CROSS REFERENCES

A further discussion of biogenic amines will be found in Section 2.2 on the basic science of psychopharmacology. Various aspects of psychoneuroendocrinology are covered in Section 25.8 on endocrine disorders. Catecholamines and other neurotransmitters in schizophrenia are discussed in Section 15.3. Other sections in this chapter discuss clinical and other features of affective disorders.

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18.4 AFFECTIVE DISORDERS: GENETICS

ELLIOT S. GERSHON, M.D.
JOHN I. NURNBERGER, Jr., M.D., Ph.D.
WADE H. BERRETTINI, M.D., Ph.D.
LYNN R. GOLDIN, Ph.D.

INTRODUCTION

HISTORY The role of genetic factors in susceptibility to major affective disorders has been supported by family, twin, and adoption studies; however, the precise nature of the genetic defects remains unknown.

Two basic strategies can be used to identify specific genetic components causing susceptibility to an illness, strategies that avoid some of the uncertainties of studying clinical diagnoses. The first strategy is to identify a biological trait that is correlated with susceptibility to a particular illness, such as an enzyme, neurotransmitter, receptor protein, or membrane transport characteristic. If a variant of such a trait can be shown to be associated with an illness in a population and also to be genetically transmitted with the illness in families, then the trait represents a specific genetic susceptibility component, although other genetic and environmental components may exist. The second strategy is to study linkage or association relationships of known polymorphic genetic loci, such as ABO blood types, to these illnesses both at the population level and within families of affected individuals. Various statistical methods are available to analyze these relationships in order to detect loci that are either directly or indirectly involved in disease susceptibility.

Both of these strategies are important for identifying genetic susceptibility components. The first strategy identifies traits where the underlying genetics are usually unknown; the second strategy identifies traits determined by single loci.

This review considers the design and application of both of these strategies to studies of the genetics of affective disorders. Current knowledge about the mode of genetic transmission of affective disorders coming from family studies of diagnoses is briefly reviewed. Then, the authors discuss methodological details of linkage and association studies and review results of their application to affective disorders. Lastly, current hypotheses about biological traits that have been studied in relation to genetic susceptibility to mood disorders are discussed.

EVIDENCE ON GENETIC TRANSMISSION Twin and adoption studies provide evidence on whether vulnerability to a disorder has a genetic component, meaning that a genetic variation in a population renders some persons more susceptible than others. Family studies provide evidence in a particular population on the degree to which a disorder is familial, on which diagnostic entities or other characteristics have shared familial transmission with a particular disorder, and perhaps, most importantly, allow testing of hypotheses on the mode of genetic transmission, such as whether one gene or many are acting and, when biological variables are studied, whether there is biological heterogeneity.

Adoption studies In a 1977 study of bipolar adoptees, Mendlewicz and Rainer found that an affective disorder (including spectrum disorder) was reported in 31 percent of the biological parents of these probands, compared with 2 percent in the biological parents of normal adoptees. The morbid risk in biological parents of bipolar patients was comparable to the risk these investigators found in the parents of nonadopted bipolar patients (26 percent) and was higher than it was in the adoptive parents of bipolar adoptees or normal adoptees (12 percent and 9 percent, respectively).

Schulsinger and Kety's 1979 Danish adoption study of suicide is of interest. The biological relatives of 71 adopted persons with an affective disorder had a disproportionate number of suicides (3.9 percent), in comparison with biological relatives of controls (0.3 percent) or with adoptive relatives of index or control adoptees (0.6 percent for each). The difference between biological relatives of affective patients and the biological relatives of controls is statistically significant at the 0.01 level. Nonpsychiatric suicide, defined as suicide with no preceding psychiatric hospitalization, also appeared to be genetically transmitted in this adoption study. Whether this entity is independent of affective disorders is not clear from the published data.

Twin studies The clear difference between monozygotic (about 67 percent) and dizygotic (about 15 percent) concordance in numerous twin studies of affective illness over a 50-year period argues strongly for heritability of affective illness. Twelve cases of monozygotic twins raised apart in which at least one twin had an affective disorder have been reviewed; in that series, eight pairs (67 percent) were concordant. Although this finding is quite similar to findings for monozygotic twins raised together, one must note the study's lack of systematic sampling for twins raised apart.

Bertelsen and her associates utilized the Danish twin register, which included all same-sex twins born from 1870 to 1920. Questionnaires were sent to twins or, if the twins were deceased, to their relatives, and this mailing was followed up with a personal interview if necessary, thus establishing a high degree of completeness of information. Zygosity was checked either serologically or, if both twins were not living, anthropometrically. It was possible to ascertain 110 twin pairs in which one or both members had manic-depressive illness (using Kraepelinian criteria). The concordance for monozygotic twins (58 pairs) was 0.67 and for dizygotic twins (52 pairs) was 0.20. This concordance is in close agreement with the data previously summarized. Concordance was higher for bipolar monozygotic probands (0.79) than for unipolar monozygotic probands (0.54). Dizygotic rates were similar (0.24 for bipolar and 0.19 for unipolar). Concordance was also related to severity of illness: Bipolar I probands showed 80 percent concordance in monozygotic twins, and bipolar II probands showed 78 percent concordance. Unipolar probands with three or more episodes of depression showed 59 percent concordance, and unipolars with fewer than three episodes showed 33 percent concordance. The unipolar data may reflect the fact that the population with fewer episodes had not yet passed through the age of risk.

Further analysis of concordant pairs of polarity revealed 11 unipolar-unipolar, 14 bipolar-bipolar, and 7 unipolar-bipolar. This result suggests some genetic specificity for polarity, but it also suggests that unipolar and bipolar illness can be associated with the same genetic make-up. These data clearly demonstrate the inherent ambiguity in biological comparisons of bipolar versus unipolar patients. At the very least, a substantial portion of unipolar patients have the same genetic and biological vulnerability as bipolar patients.

The familial concentration of affective disorders is evident in recent case-controlled studies. Relatives of bipolar and unipolar patients have higher prevalence of bipolar and unipolar disorder than is found in relatives of controls. Major depression (unipolar disorder) is the most frequent affective disorder in families of both unipolar and bipolar patients; this

frequency implies overlap in the familial causes of both forms of disorder. The same implication is also present in the twin data in a smaller number of individuals at risk.

There is an inconsistency in reported prevalences in relatives in family studies, and this inconsistency necessitates a methodological digression on family studies. The inconsistency is present even when one considers only studies with explicit diagnostic criteria and direct examination of relatives. Some of the discrepancies are undoubtedly due to differences in procedures and criteria, as well as to population differences; yet, could the inconsistencies reflect a basically unreliable methodology? In collaborative studies, good reliability between centers can be established, and very similar prevalences in relatives can be found. Within studies that had good reliability and that used quite similar procedures, cognitive or cultural factors have been shown to lead to differences in diagnostic rates in family studies. Urban setting, younger generation, and American nationality are associated with higher diagnostic rates for unipolar disorder.

The fact that cognitive or cultural factors appear to be a general aspect of morbid risk estimates has several implications. First, there is not a "true" rate of diagnosable affective illness in the population or in relatives of patients. The rates may be a function of procedures and criteria, of the culture of the population in which they are observed, and of genetic factors. Second, clinical anamnestic criteria now available do not, across populations, consistently define a phenotype for affective illness, even though these procedures can be reliably applied. The same arguments apply to the variations between twin studies.

In the authors' own recent data, in a metropolitan American setting, the lifetime prevalences of major affective disorders in first-degree relatives of normal controls, unipolars, bipolars, and schizoaffectives were 7 percent, 20 percent, 25 percent, and 37 percent, respectively. These data show that the affective disorders are fairly common and that within the population they are concentrated to a great extent in a limited number of families.

THE CLINICAL SPECTRUM OF AFFECTIVE DISORDERS The clinical genetic spectrum of bipolar disorders can be constructed by comparing the prevalence of illness in relatives of patients with the prevalence in relatives of controls.

Schizoaffective disorder Reference is made here to patients with episodic as opposed to chronic periods of schizophreniform psychosis along with affective symptoms and to patients with some episodes that appear schizophrenic and others that appear affective in nature, again episodic over the lifetime. Most studies of first-degree relatives of patients with schizoaffective illness have shown more affective illness, particularly bipolar illness, and (to a lesser extent) schizophrenia in the relatives than schizoaffective illness. The authors and colleagues found that, among 84 first-degree relatives of schizoaffective probands, the morbid risk is 6.1 percent for schizoaffective disorder, 10.7 percent for bipolar I disorder, 6.1 percent for bipolar II, 14.5 percent for unipolar, and 3.6 percent for schizophrenia.

Although schizoaffective probands tend to have a high frequency of affective illness in relatives, and a low incidence of schizoaffective illness, the twin studies present a very different picture. In McCabe's 1975 review, 13 out of 44 monozygotic twins versus 1 out of 45 same-sex dizygotic twins were concordant for type of illness. This definition included as concordant those persons who were ill with reactive schizophreniform psychosis, as well as schizoaffective psychosis. Although the twin studies show that the same form of psychosis appears to be genetically transmitted, this fact does not appear true in the family studies.

Where the monozygotic twin concordance appears so much greater than the concordance among first-degree relatives, the data may be reflecting a peculiar form of inheritance. The phenomenon may be produced by interaction among several loci in such a way that there is greatly increased concordance in monozygotic twins, as compared with concordance in dizygotic twins and other first-degree relatives. This concordance is produced because monozygotic twins will be identical by descent at all loci, but the chances, for example, of two siblings being identical by descent at a given locus are one-half. The probability of being identical by descent at n loci is therefore 0.5^n, which becomes a vanishingly small number as the number of loci involved increases. An example of this type of inheritance appears to be found in the visual evoked response.

As applied to schizoaffective disorder, this speculation suggests peculiar genetic factors that cause the psychosis to have a schizoaffective expression, since there is a high twin concordance. These factors, in turn, appear to be superimposed on the genetic diathesis for affective illness, since this disorder is consistently the most frequent one in relatives of schizoaffective patients.

Alcoholism There has been disagreement in the literature whether alcoholism tends to concentrate in the families of persons with affective illness. This controversy may be resolvable by studying affective probands who have no alcoholic difficulties themselves.

In the authors' own and other current data, there is no increase in alcoholism in the relatives of nonalcoholic affectively ill probands compared with the relatives of controls. Although bipolar illness and alcoholism are not uncommonly found in the same person, alcoholism by itself without affective disorder does not appear to belong in the genetic spectrum of bipolar manic-depressive illness.

Anorexia nervosa In 1977, Cantwell reported in a family history study of anorectic patients that an excess of affective disorder was present in relatives, and this fact has been repeatedly corroborated. Recently, Winokur and his co-workers studied 25 anorectic women and 192 of their first and second-degree relatives. A group of 25 age-matched women with no history of anorexia or depression were used as controls. Of the relatives of the anorectic women, 17.7 percent had unipolar illness, and 4.7 percent had bipolar illness (not age corrected). The corresponding figures for controls' relatives were 9.2 percent and 0.6 percent. The difference in total incidence of affective illness was significant ($P < 0.0005$), suggesting a genetic relationship between the two disorders.

The authors and their colleagues have had similar findings, a modest amount of anorexia in relatives of anorectic patients (2.0 percent) and as much affective disorder as in relatives of bipolar patients (8.3 percent bipolar and 13.3 percent unipolar). In relatives of bipolar patients, however, there is very little anorexia (0.6 percent). It appears that anorexia has a unique familial vulnerability factor, possibly genetic, which is superimposed on a genetic tendency to bipolar and unipolar affective disorder. This tendency appears to be even less common than the similar tendency to schizoaffective disorder.

Other diagnoses Evidence from family studies suggests that cyclothymic personality may be related to bipolar affective disorder. Hyperactive syndrome of childhood attention deficit disorder, agoraphobia, and anxiety disorder have also

been hypothesized to be related to affective illness. Nonpsychiatric suicide may belong in the clinical spectrum as noted above.

Childhood manifestations of vulnerability are of research interest, but none are so far established.

MODE OF GENETIC TRANSMISSION

GENETIC MODELS OF AFFECTIVE DISORDERS Hypotheses of genetic transmission of an illness can be tested using familial data. In the past few years, sophisticated statistical models have been applied to test hypotheses of single major locus transmission, multifactorial (or polygenic) transmission, and mixed major locus-polygenic transmission. Some of these models can take variable age of onset and nonrandom ascertainment into account and have been applied to data on psychiatric disorders. Applications of these models to affective illness have not been consistent with autosomal or X-chromosome single locus transmission of affective disorders.

Alternatively, multifactorial transmission of a genetic disease can be modeled as a linear combination of genetic and environmental factors (liability factors), each having a small effect. There can be one or more thresholds on a hypothesized liability scale that determine whether an individual expresses a particular trait (illness). In this multifactorial approach, there is a polygenic component—that is, many genes—with random or familial environmental variation. The models will predict the prevalence rates in various classes of relatives of ill persons and can be compared with observed prevalences.

Data on prevalences in relatives of patients with affective disorders have usually been consistent with multiple threshold polygenic models. In some studies, prevalences of the affective diagnoses in relatives of patients with affective disorders are consistent with a multifactorial liability with three thresholds corresponding to severity of illness (risk in relatives of unipolar patients < risk in relatives of bipolar patients < risk in relatives of schizoaffective patients). Thus, the degree of genetic transmission is related to the severity of illness as modeled on a continuous liability scale.

The biological implications of this multifactorial model are that the bipolar vulnerability includes all of the unipolar genetic vulnerability, plus added factors that may be genetic or environmental. Additional evidence supports the placement of schizoaffective disorder at the severe end of the spectrum. In other words, the model predicts that there are more genetic abnormalities to be found in bipolar or schizoaffective patients than in unipolar patients. This prediction corresponds with the shared intuition of many clinical investigators who have focused their biological studies on bipolar and schizoaffective patients, even though unipolar illness is the more common form of affective illness.

Because multifactorial hypotheses are consistent with the prevalences of psychiatric disorders in relatives and because major locus hypotheses are inconsistent with the transmission within families, the possibility that there are major loci causing vulnerability to these disorders is not ruled out. A single gene effect may not be detectable from pedigree data unless a closely linked marker locus is studied. The historical example of diabetes mellitus, long thought of as a classical multifactorial disorder, but recently discovered to have two forms with single locus determinants, should be borne in mind. In the remainder of this paper, therefore, the identification of genetic components of affective disorders through studies of genetic marker loci and of biological traits with unknown mechanisms of inheritance is discussed.

SINGLE LOCUS MARKERS IN AFFECTIVE DISORDERS

The methodology used for linkage and association studies is discussed below in some detail, followed by a discussion of findings in the literature. This detail is allowed for methodology because, as the number of informative polymorphic loci increase rapidly from DNA technology, thereby expanding present knowledge of the human genome, these strategies will take on greater importance than they had previously.

POPULATION ASSOCIATION OF AN ILLNESS WITH A GENETIC MARKER LOCUS Studies of populations of patients having both common and rare diseases have revealed associations of certain diseases with genetic marker phenotypes. The genetic traits most commonly studied are ABO blood types and human leukocyte antigen (HLA) types. HLA consists of several loci on chromosome 6 that code for antigens on leukocytes and other immune function measurements. There are a large number of alleles at each locus. The loci most commonly studied are the serologically measured *A* and *B* loci. A *haplotype* is defined as the set of antigens carried on a single chromosome. The relationship of HLA antigens to various diseases, including major psychiatric disorders, has been studied extensively because of the high degree of polymorphism of these loci and the reports of numerous diseases associated with specific HLA types.

The significance of an association can be determined by a χ^2 statistic from a 2×2 table (disease present or absent by marker trait present or absent). If, however, more than one marker trait is tested, e.g. large series of HLA antigens, then the significance level must be multiplied by the number of tests.

There are several explanations for the existence of an association between a genetic marker trait, such as HLA, and a disease. First, the marker trait may play a role in disease susceptibility, although other genetic and environmental components may be involved. This situation is likely to be true in the case of ankylosing spondylitis, where 90 percent of patients with the disease have a specific HLA type (B27), and only 10 percent of controls have that type. Second, a gene closely linked to the marker trait may cause susceptibility. In general, if a disease susceptibility gene is chromosomally linked to a marker locus, there should be *no* association between alleles at the two loci in the population unless there is some disequilibrium between them. *Disequilibrium* refers to the case where particular allele combinations of the two loci occur in individuals more frequently than expected by chance. Disequilibrium can be caused by natural selection for certain allelic combinations, by recent admixture of populations, or by chance genetic drift. It has been shown to be extensive among loci of the HLA region; therefore, associations of a disease with an HLA antigen may be due to the presence of a disease susceptibility locus in the HLA region that is in disequilibrium with HLA. Third, such an association may be an artifact due to population stratification. To illustrate this point, suppose that there is *no* association between a disease and trait *X*; however, diseased individuals come from a subpopulation that has a high frequency of trait *X*, and control individuals come from a subpopulation that has a low frequency of trait *X*. A comparison between the patients and controls will show an association between the disease and trait *X*.

Many population stratifications are obvious (such as racial or ethnic) and usually are controlled for in association studies, but not all of such heterogeneity is obvious. It is known that there is significant geographical variation in HLA antigens

and other markers. Many modern populations are genetically heterogeneous because a recent mixture of populations that differ in gene frequencies causes stratification. It is very important to control for stratification as much as possible when carrying out and evaluating association studies. This point will be returned to later on when the authors review published studies.

LINKAGE BETWEEN A DISEASE SUSCEPTIBILITY LOCUS AND A GENETIC MARKER LOCUS Loci that are situated close to each other on the same chromosome do not assort independently and are said to be linked. Rearrangement of alleles between pairs of homologous chromosomes by crossing over (called recombination) occurs during meiosis, however, so that alleles at linked loci are not always transmitted together. The further apart two loci are situated, the more chances they have to recombine in this way. When recombination between two loci occurs 50 percent of the time, this is not distinguishable from independent assortment. The distance between two loci is expressed as the percentage of recombination (θ) between them.

Linkage analysis is important in studying the underlying genetics of a disease or trait. If linkage between a disease locus and a marker locus becomes well established, then this linkage defines a specific genetic disorder that eventually will be mapped to a particular region of the human genome. Such information can potentially be useful in predicting disease susceptibility in individuals from segregating families.

Several types of polymorphic genetic marker loci are available for linkage studies. The ones most commonly used are (1) red cell antigens, such as ABO, Rh, and MNS, and leukocyte antigens (HLA) that are detected serologically and (2) red cell and serum enzymes and proteins that are detected electrophoretically. Additionally, although not used frequently, several polymorphisms in chromosomal banding patterns can be detected by high resolution banding techniques. Unfortunately, the red cell and serum markers generally used (about 30) cover only a small proportion of the human genome. For example, the chance that one of 30 randomly distributed marker loci will be relatively close—that is, $\theta < 20$ percent—to a disease locus has been estimated to be about 30 percent. In addition, the probability of detecting a linkage also depends on the size, structure, and number of families in the sample. Currently, polymorphisms are being identified at the DNA level by using restriction enzymes, called restriction fragment length polymorphisms (RFLP's). It is expected that, within the next several years, enough RFLP's will be available to cover the entire genome. Thus, it should eventually be possible to map any single locus that plays a role in a disease susceptibility. It is not yet clear how large a role a gene must have in determining a trait in order to be mappable to a point on the human genome. It is conceivable, however, that several loci affecting a single trait will be identifiable.

Two methods of detecting linkage can be used depending on the type of data available and the assumptions that can be reasonably made. If the data consist of complete nuclear families or larger pedigrees, then it is possible to apply the lod-score method. Methods have also been developed to detect linkage in samples of affected pairs of siblings (sib-pairs). These two methods will be discussed in terms of the underlying assumptions and relative advantages and disadvantages.

Lod-score method The lod-score method, originated by Newton Morton in 1955, is a means of testing the hypothesis of linkage between two loci when the mode of transmission of each locus is known. The underlying assumptions include the following: (1) The parameters, gene frequency and genotypic penetrances, for the disease locus and marker locus are known; (2) there is *no* population association between the disease locus and marker locus. Under these assumptions, one compares the probability of observing the pattern of segregation of the two traits in a family if there is linkage as against the probability of observing the family if there is no linkage. The probability of linkage is expressed as a function of the recombination fraction (θ) where θ is some value between 0 and ½. The probability of no linkage is the probability that the two loci are segregating independently; that is, $\theta = ½$. This odds ratio is expressed by a statistic called the lod score, or log of the odds ratio, and is defined as a ratio:

$$\text{Lod score} = \log_{10} \frac{\text{probability of observing a family given } \theta < ½}{\text{probability of observing a family given } \theta = ½}$$

A lod score of 1.0 means that linkage is 10 times more likely than no linkage. The lod scores for small families can be done by hand or, in simple cases, by using tables. For larger or more complex families, computer programs are generally used to perform the calculations. In practice, for each family the lod score is evaluated for several values of θ. Because the scores are in $\log_{10}$ units, summing across families is equivalent to multiplying independent probability ratios and is legitimate. If linkage is present, the best estimate of θ is that value of θ that results in the highest lod score. Data can be evaluated sequentially after each sample of pedigrees is collected. A score of 3.0 is the generally accepted cut-off value for acceptance of linkage and −2.0 is the cut-off value for rejection of linkage. If the score is intermediate, then more families should be collected until the hypothesis can either be accepted or rejected. This convention has generally been followed in linkage studies. Use of these absolute cut-off points, however, may not always be appropriate; when tests of linkage of a disease locus to many marker loci are made, significant lod scores may occur by chance in a single study.

Sib-pair method The use of samples of affected sib-pairs for linkage analysis may be desirable because fewer assumptions are required. The idea behind the method is that, if a marker locus is linked to a disease locus, then affected pairs of siblings will have the same genotype at the marker locus more often than expected by chance. Because only affected siblings are used, this method is especially useful for disease susceptibility loci that are thought to have low penetrance. Although general in theory, this method has been mainly developed to apply to problems of detecting linkage to the HLA loci. Because there is so much polymorphism in the HLA region, each parental chromosome has a different set of HLA alleles, or haplotype. Thus, it is usually possible to determine whether affected sib-pairs share exactly 2, 1, or 0 haplotypes identical by descent (IBD) at the marker locus. If there is *no* linkage, then the proportion of affected sib-pairs sharing 2, 1, and 0 haplotypes is ¼, ½, ¼, respectively. If linkage is present, then this distribution is skewed, so that more than 25 percent of affected sib-pairs have identical haplotypes. The simple hypothesis of linkage can be tested by comparing the observed IBD distribution in a sample of independent affected sib-pairs with that expected when there is no linkage. The affected sib-pair method has been further developed in order to make some inferences about the mode of inheritance of the disease trait and the recombination fraction between the disease and marker loci. In theory, it is also possible to use unaffected pairs and unaffected-affected pairs of siblings for this test; however, these types of sib-pairs do not contribute very much

information about linkage, because the genotype of the unaffected sibling at the trait locus is uncertain.

Comparison of methodologies of linkage analysis The choice of methods to use for linkage analysis will depend on several factors. For some diseases, it may be easier to collect data on a sample of affected sib-pairs than on complete families. Although the lod-score method is easily applied to small nuclear families, it is most powerful for larger multigenerational families, which are generally more difficult to study. As stated previously, however, the affected sib-pair method is most efficient for highly polymorphic loci, such as HLA, and will require larger sample sizes in the case of other loci. Most importantly, the underlying assumptions required for these methods are different. For the lod-score method, the underlying genetic parameters (gene frequency, penetrances) *must* be specified. Unfortunately, for many diseases studied, the mode of transmission is not known and is often guessed in order to calculate lod scores. Incorrect specification of the model, however, can give the wrong results, and variation in the unknown model parameters can also affect the results.

As stressed previously, no such assumptions are needed to test the hypothesis of linkage in affected sib-pairs, and this test is therefore most appropriate when the exact mode of transmission of the disease locus is unknown. If preliminary evidence for linkage is obtained from sib-pairs, it is possible to estimate genetic parameters under certain models and thereby make some inferences about the mode of transmission of the disease.

Another problem that needs to be considered with either method is possible genetic heterogeneity of the disease under study. Because families are pooled for both methods, it is assumed that the same disease locus is segregating in each family. If there is heterogeneity, then such pooling of families will lead to erroneous results. It is possible to test for heterogeneity of linkage; however, large families are generally needed to be able to detect significant heterogeneity.

These deviations from simplifying assumptions must be taken into account when performing linkage analyses. In psychiatric disorders particularly, the validity of most of the simplifying assumptions is unknown; that is, the mode of transmission of illness is unknown, the illnesses may be genetically heterogeneous, and assortative mating may exist. In addition, the "ill" phenotype cannot be exactly defined, because there are numerous theories with regard to which diagnoses should be included in a particular spectrum.

ASSOCIATION AND LINKAGE STUDIES IN AFFECTIVE DISORDERS

Association studies ABO LOCUS Several studies have reported the frequencies of ABO types in patients with an affective disorder (or subgroups of patients) as compared to control populations. A few studies have found a higher frequency of blood type O in manic-depressive patients than in controls, but other studies have been conflicting. Some studies have found no differences between patients and controls. It has been suggested that many of the significant results reported in the literature are artifacts due to skewed patient population samples. In one study, it was found that the entire population of psychiatric patients had different ABO frequencies than the control population. If manic-depressive patients were compared to all other psychiatric patients, there were no significant ABO differences. This finding demonstrates the potential effect of population stratifications on association studies.

HLA LOCI A Danish study by Shapiro and associates of HLA types in patients with affective disorders found that the patients had a significantly higher frequency of HLA BW16 than a control population. This finding generated some excitement; unfortunately, subsequent studies were unable to replicate the association. Associations with other antigens were reported, but none were statistically significant after correction for the number of antigens tested. The fact that HLA BW16 was found to be higher is interesting because this antigen is found with much higher frequency in Ashkenazi Jewish populations than in other European Caucasian populations. Ashkenazi Jews also have a higher frequency of manic-depressive illness than other European populations. Studies that compared HLA types in Ashkenazi Jewish patients to ethnically matched controls found no differences. In most of the HLA studies reported, BW16 is slightly higher in patients than in controls. This finding may be another example of population stratification, if the samples of patients are enriched with individuals of Ashkenazi Jewish origin.

Linkage studies Studies of linkage of affective disorders to genetic markers have included loci both on the X chromosome and the autosomes. The X-chromosome studies were motivated by an initial finding that, in bipolar patients' families, there was a high rate of mother-son transmission of illness, virtually no father-son transmission, and a higher proportion of females affected than males. These findings are consistent with the pattern of an X-linked dominant gene; however, subsequent family studies did not always replicate this pattern. The results of linkage studies with X-chromosome markers have stirred considerable controversy. Other autosomal marker loci have been studied, with special emphasis on the HLA loci. In the two sections below, the evidence for linkage to X-chromosome and autosomal markers will be reviewed.

X-CHROMOSOME MARKER STUDIES In the late 1960s and 1970s, Winokur and, later, Mendlewicz reported linkage of bipolar affective disorder to markers on the X chromosome, including color blindness (CB), G6PD, and Xg blood group; most of the studies examined the CB locus. Although CB and G6PD are closely linked on the X chromosome, Xg is located at an entirely different region. Thus, linkage of the same gene to both loci is incompatible. In addition, studies of CB and Xg loci in other series of pedigrees did not confirm the linkage hypothesis.

It has been argued that, on the basis of a reanalysis of all the published X-chromosome data, incorporating age of onset into the linkage analysis, there is heterogeneity of the illness so that a proportion of families are segregating for a gene linked to the CB locus of the X chromosome. This interpretation is controversial because most of the families favoring linkage are from one group of investigators, and most of the families favoring nonlinkage are from another group of investigators. Virtually any disagreement between investigators can be interpreted as heterogeneity. More data are needed, and may be available in the near future, with the use of DNA polymorphisms in the CB region of the X chromosome. If enough polymorphisms can be identified, virtually all families will be informative for X-chromosome linkage.

AUTOSOMAL MARKERS A few studies have examined possible linkage relationships of autosomal markers, such as red cell antigens and serum proteins, to affective disorders, but no consistent findings have emerged. In addition to studies of association of HLA types with affective disorders in populations, there has also been substantial interest in linkage of affective disorders to the HLA region. There have been studies

of HLA types in samples of affected sib-pairs, as well as in families. Results from some studies favor a linkage hypothesis, but the majority of studies do not support linkage. Moreover, there have been methodological criticisms of the positive studies. This controversy is not yet resolved, but it appears unlikely that HLA plays a major role in susceptibility to affective disorders.

NEW DEVELOPMENTS Advances in techniques of identifying genetic variation make the possibility of identifying susceptibility loci for psychiatric disorders more promising, even in light of heterogeneity or diagnostic uncertainties. These new methods will greatly expand the number of genetic marker loci that can be used for linkage and association studies.

TWO-DIMENSIONAL GEL ELECTROPHORESIS Techniques have been developed to screen large numbers of proteins for polymorphisms by two-dimensional gel electrophoresis. This technique, along with computer densitometry, allows several hundred proteins to be resolved on a single gel. New protein polymorphisms can thus be identified to use as linkage markers or to study protein variation related to function.

In one study, samples of autopsy brain tissue from individuals with various psychiatric and neurological disorders were examined. A common single locus, two-allele polymorphism in a brain protein, called Pc 1 Duarte, was identified and found to be associated with multiple sclerosis and depressive illness. This finding is a provocative one, but unfortunately, this protein cannot be identified in peripheral tissues, and therefore, its study is limited to autopsy material. Attempts are currently under way to develop a DNA probe that codes for this protein. If such a probe were available, then linkage and association studies could be carried out in living patients and families. Because this polymorphism was found to be common in normal individuals, it may represent a secondary susceptibility gene.

RECOMBINANT DNA TECHNIQUES New recombinant DNA technologies have revolutionized the study of human genetic diseases. These techniques can be applied to problems in psychiatry.

As mentioned, DNA probes are being developed that will detect polymorphisms in DNA sequences when restriction enzymes are used to cut the DNA. It is expected that within the next several years, enough polymorphisms will be identified in this way to cover the entire human genome. It is estimated that approximately 150 equally spaced polymorphisms would assure that no trait locus would be more than 10 recombination units away from a DNA marker locus. Theoretically, any known locus for a disease or trait will be mappable to the genome. The use of these markers to map illnesses which are *known* to be caused by single major loci is relatively straightforward. In the case of psychiatric disorders, where the modes of genetic transmission are less defined, these techniques are still applicable, but with the same cautions as in any linkage analysis. In addition, if a lod-score analysis were applied to any disorder using 150 markers, there would probably be several markers linked by chance alone in any one sample, especially if the classification of ill-well phenotypes is varied. It will be necessary to confirm any suspected linkages in new samples and *not* make inferences about linkage from a single sample, or even a single pedigree.

Another application of this technology is the study of DNA variation, using probes for specific substances. Currently, DNA probes exist for regions that code for neuroactive peptides, such as pro-opiomelanocortin (POMC)—which is the precursor for adrenocorticotropic hormone (ACTH), β-lipotropin hormone (LPH), and endorphins—polyenkephalins, somatostatin, and arginine vasopressin. Restriction enzymes could be used to identify polymorphisms in these regions that may be associated with particular illnesses where there is an abnormality related to the function of these proteins. For example, a well-known case in point is sickle cell anemia. Prior to the developments in recombinant DNA techniques, it was known that sickle cell disease was a result of a single amino acid substitution in the β-globin chain of the hemoglobin molecule. Using a DNA probe for the globin region and certain restriction enzymes, it has been possible to identify polymorphisms near and at the site of the base pair substitution in the DNA itself. These polymorphisms can be used to detect sickle cell disease *in utero*, a major advance in human clinical genetics. Even though the genetics of the major psychiatric disorders are not well defined, this approach has some promise because hypotheses about the role of genes coding for specific neuroactive substances in disease etiology can be tested.

BIOLOGICAL VULNERABILITY TRAITS

INVESTIGATIVE STRATEGIES Relatively few studies have attempted to identify biological factors that are inherited in these disorders. To make this identification would require a genetic marker that, applied to each individual in a pedigree, successfully predicts who is at risk and who is not. Ideally, one would seek a biological variant, such as an altered protein, that could be assigned a specific locus on an identifiable chromosome. Because stable biochemical differences suggest genetic differences, however, virtually any biological finding that was clearly associated with the tendency to affective illness in a subgroup of patients might be studied as a possible genetic trait.

The converse strategy is also valid: Genetic strategies may be used to demonstrate the validity of a particular biological component of the affective disorders, even in the absence of an established mechanism of genetic transmission. Criteria for establishing a genetic vulnerability trait for an illness have been proposed:

1. The characteristic, either quantitative or qualitative, must be associated with an increased likelihood of the psychiatric illness. The converse, that persons with the illness should generally show the characteristic, need not be true, because there may be biological heterogeneity in the illness.
2. The characteristic must be heritable in general and, as observed, must not be a secondary effect of the illness.
3. The characteristic must be demonstrable in the well state, either by direct observation or by experimental manifestation, so that it is possible to determine its presence independently of the illness and to evaluate well relatives.
4. The illness should be associated with the trait within pedigrees. Because the twin and family data strongly suggest that some persons with the genetic tendency to mood disorder will be phenotypically well, it is not necessarily true that all well relatives should not show the putative marker. The critical prediction would be that, if a trait is a *necessary* one for the illness, frank illness should not be transmitted without the marker, except for sporadic cases; if, in a pedigree, some ill persons show the marker and significant numbers of others do not, the illness can be transmitted without the trait. If the finding is only more common in ill relatives, it may be a contributing factor, but not a necessary (primary) factor.

An alternate strategy has been proposed as the "biochemical

high-risk paradigm." Here, a large population sample is studied on a quantitative measure for a putative biochemical marker. Persons in low and high extremes of the measurement are compared for family history of psychiatric illness. If the marker is valid, family history of illness will cluster at one extreme. This strategy, however, is less robust than the pedigree strategy detailed above because it loses power if there is biological heterogeneity in the illness.

Phenomena that are demonstrable only in the presence of active illness have limited usefulness in the genetic investigation of an illness with incomplete penetrance. For example, if a urinary metabolite is decreased or if cortisol is increased only during episodes of illness, it is impossible to determine whether well relatives or controls would have the same finding.

State-dependent phenomena can be studied, however, to see whether they are associated with familial affective disorder, or whether they are predictive of increased morbid risk in relatives. Recently, this strategy has been applied to CSF 5HIAA, dexamethasone suppression, and other variables. Some of these studies can be criticized for the quality of family history data on which they rely. For example, unless virtually all relatives are examined, it is grossly unreliable to classify patients as family history negative. Furthermore, the genetic meaning of presence or absence of family history is not at all apparent, especially for disorders as common in the population as affective disorders. Counting the *number* of known ill relatives for separate groups of patients, and not the *proportion* of relatives who are ill, is also not meaningful. Family history in relation to biological findings in patient groups is a strategy that can have merit, but in some studies, the data offered have been a combination of extremely sophisticated biological measurements and family history information based on insufficient data.

FINDINGS Stable characteristics that have been examined in the hope of identifying a marker—where there are at least some data on genetic variation—include measures related to monoamine metabolism (enzymes and metabolites); cholinergic pharmacological response and cholinergic receptor density; plasma and CSF GABA; ^{3}H-imipramine binding, which is related to serotonin transport; and indices of cation transport (Table 18.4–1).

The findings on enzymes of monoamine metabolism and on CSF 5HIAA are summarized in Table 18.4–1. CSF 5HIAA and the Pc 1 Duarte protein each may yet prove to be a valid marker in a proportion of pedigrees, but appropriate investigative strategies have yet to be developed. In the case of CSF 5HIAA, it will be difficult to do pedigree studies because individuals are often reluctant to undergo the lumbar puncture procedure. Plasma GABA, whose relation to CNS GABA is undocumented, distinguishes patients from controls and is apparently heritable, and further study of its validity as a vulnerability marker is warranted.

The ^{3}H-imipramine (^{3}H-IMI) binding site in platelets is similar to, or associated with, a serotonin transport protein. This system resembles the serotonin uptake system in brain. Initial reports of reduced numbers of binding sites in depression raised interest in the density of sites (B_{max}) as a possible trait marker in affective illness. Variation in B_{max} for ^{3}H-IMI binding is highly correlated in monozygotic twins, suggesting that this characteristic may be heritable. Recent data suggest that binding is not decreased in euthymic medication-free patients. If B_{max} is normal in euthymic patients, then the reported decrease is a state-dependent phenomenon, as opposed to a trait marker for vulnerability to affective illness.

FAMILY STUDIES OF BIOLOGICAL TRAITS Only two of the studied characteristics have suggestive data on segregation of a biological abnormality with illness: lithium erythrocyte/plasma ratio and muscarinic acetylcholine receptor density.

Lithium transport Dorus and associates have investigated the genetics of lithium transport and its relation to the genetics of manic-depressive disorder. Data on 291 individuals from 120 families of normal controls, and on 66 relatives of 31 bipolar I patients, of whom 16 had major affective disorder and 28 had minor affective disorder, were recently reported. Of the relatives, 11 with major affective disorder and 2 with other diagnoses had been psychiatrically hospitalized. The 31 bipolar I patients, however, were not studied for their own lithium transport parameters. This omission is unfortunate,

TABLE 18.4–1
Current Status of Proposed Genetic Vulnerability Traits for Affective Illness*

Putative Markers	*Patients Differ from Controls*	*State Independent*	*Heritable*	*Segregates with Illness*
Cation transport				
Lithium erythrocyte/plasma ratio	Yes (most studies)	Possibly	Yes—single locus and multifactorial	Possibly
Monoamine related enzyme activities				
Plasma DBH	No	Yes	Yes—single locus	No
Erythrocyte COMT	No	Yes	Yes—single locus	No
Platelet MAO	Yes	Yes	Yes—single locus	No
Serotonin transport protein				
Platelet ^{3}H-imipramine binding	Yes	No	Possibly	No data
Monoamine and amino acid metabolites				
CSF 5HIAA	Yes	Yes	Possibly	Unknown
Plasma GABA	Yes	Yes	Possibly	No data
Muscarinic cholinergic studies				
Early induction of REM sleep by arecoline (muscarinic agonist)	Yes	Yes	Possibly	No data
Fibroblast muscarinic receptor density	Yes	Yes	Yes	Possibly

DBH—dopamine-β-hydroxylase
COMT—erythrocyte catechol-*O*-methyltransferase
MAO—platelet monoamine oxidase
CSF—5HIAA—cerebrospinal fluid 5-hydroxyindoleacetic acid
REM—rapid eye movement
GABA—γ-aminobutyric acid

* From Gershon E S, Nurnberger J I, Jr, Nadi N S, Berrettini W H, Goldin L R: Current status of genetic research in affective disorders. In *The Origins of Depression: Current Concepts and Approaches*, Dahlem Konferenzen 1982, J Angst, editor, p 187. Springer-Verlag, Berlin, 1983.

because the 31 probands constitute the majority of major affective disorder patients in these families and because the key issue of the relation of major affective disorder to lithium transport in relatives in these data remains imperfectly resolved.

The analysis of lithium ratio inheritance per se is a straightforward analysis of a quantitative trait, based on 291 individuals from normal families. Solutions that include all the parameters of both major gene and polygenic inheritance are accepted from among similarly complex hypotheses that are rejected. The major component of inheritance appears to be multifactorial, and a single locus component is also present. Using the same model on a linear combination of the lithium ratio and diagnosis, the null hypothesis of no single locus and no polygenic transmission was rejected. The rejected model, however, was mathematically much simpler (had fewer parameters) than the other models. There was a lack of discrimination among various specific genetic hypotheses, and most of the affected relatives had lithium ratios within the lower distribution; that is, the distribution found in the normal families. If the diagnostic trait was ever hospitalized, the discrimination was improved, but there were only 13 such relatives, 2 of whom were not diagnosed as having an affective disorder.

Nonetheless, this study is a most important one. If replicated, with larger numbers of lithium studies in ill individuals, it would have important diagnostic and preventive implications.

Acetylcholine Interest in acetylcholine in affective disorders stems from the work of Janowsky and colleagues, who proposed that depression is accompanied by a relative increase of cholinergic to adrenergic activity in some part of the central nervous system (CNS). It has been demonstrated that the cholinergic REM induction test (CRIT) distinguishes bipolar patients from normal controls, even when patients are tested in the well state. In this test, a small dose of a cholinergic agonist, arecoline, induces a rapid eye movement (REM) sleep period. At low doses of arecoline, a REM sleep period is induced in affective patients, but not in controls. REM inducibility by this procedure is also highly correlated in monozygotic twins. These findings have suggested the possibility of increased muscarinic receptor sensitivity as a pathophysiological vulnerability marker.

Muscarinic receptors can also be studied clinically in cultured fibroblasts. In 18 affective illness patients and 13 ill relatives, muscarinic receptor density was considerably higher than in 12 normal controls, with little overlap. As reviewed by Nathanson, in muscarinic receptors,

> studies with cultured cells have demonstrated that the loss of receptors from the cell surface is accompanied by a reduction in physiologic responsiveness to further cholinergic stimulation.

If normal persons are considered analogous to the cell lines with decreased receptors, this suggests a possible relation between increased fibroblast receptor number in affective patients and the increased cholinergic responsiveness in sleep studies of remitted affective patients.

Increased muscarinic receptors in the CNS in affective illness was also suggested by a report of increased muscarinic receptor ligand binding in the brains of suicide victims; however, two more recent series did not replicate this finding.

A muscarinic receptor vulnerability hypothesis to affective illness may be proposed based on the evidence that there is increased fibroblast muscarinic receptor density and increased CNS response to muscarinic stimulation in affective patients, that these findings are state-independent and heritable, and that the increased fibroblast receptor density is associated with illness in relatives of patients. In this hypothesis, increased muscarinic receptor density, characteristic of some CNS and peripheral cells, is a predisposing factor to affective illness.

Both hypotheses, on lithium ratio and on muscarinic receptor density, are supported by only small numbers of patients or ill relatives or both. Further studies of segregation within pedigrees are required, for these and other biological variables.

CLINICAL APPLICATIONS

In clinical practice, several issues arise with some frequency as a result of greater sophistication of the consumers of medical care and as a result of a widespread belief among patients and relatives that all serious psychiatric illness is genetic. These issues are (1) the risk to offspring of patients, (2) the possibilities for prevention, (3) the choice of treatment in view of family history, and (4) requests for genetic counseling.

In the authors' recent study, the lifetime risk of affective disorders to 614 offspring of one affectively ill parent (largely bipolar) was 27 percent. The risk to 28 offspring of two ill parents was 74 percent. Great precision from an estimate based on 28 persons at risk would not be expected, but other studies also suggest the risk to be at least 50 percent. These risks are for adult affective illness. Systematic studies of diagnosis *in childhood* of these offspring are only now beginning; however, the clinician may be presented with demands for advice on childhood interventions by parents with an affective disorder. The authors do not know of any therapeutic intervention that will reduce the risk of illness. The only interventions they would suggest is early recognition and treatment of major affective disorder if it does develop. Their experience has been, especially when the onset is in adolescence, that treatment may be avoided for years because of denial, with unfortunate consequences. Teenage suicides are reported in some of these families.

Choice of pharmacological treatment may be helped by family history. In one study, unipolar patients with a family history of bipolar illness were more likely to be lithium responders than the patients without such a family history. History of response to a therapeutic agent in a close relative is good reason to try the same agent in a newly presenting patient.

Requests for genetic counseling will arise. These requests should be looked on as problems in short-term psychotherapy. The goals may be delineated as follows: (1) realistic and appropriate appreciation of the patient's (or spouse's) family history, (2) communication of current knowledge on morbid risk, (3) coping with anxiety and narcissistic injury related to risk, and (4) planning for appropriate response to risk.

In counseling, the patient's spouse must also be considered. A tendency for assortative mating—tendency for persons with similar affective disorders to marry—has been reported repeatedly. Whether this tendency increases the genetic risks is not known, but it does give a peculiar quality to many of the marriages. Divorce is often attributed to symptoms of the illness, usually mania. Occasionally, the clinician will be confronted with blunt questions: My fiancé is a manic-depressive. Should I marry him? My wife is a manic-depressive. Should we have children? Answering these questions requires clinical skill and compassion. In Targum and co-workers' questionnaire to a group of married bipolar patients and their "well" spouses, one of the questions asked was, "If you had known then what you know now, would you have married?" Nine out of ten of the bipolar patients said yes, but more than half of the spouses said no.

Unfortunately, no test can now be given that identifies persons at risk of developing illness or producing an ill offspring. Although there are some promising developments discussed above at some length, none of them are at the point where clinical application is appropriate. Studies of young persons at high risk for developing an affective disorder, on the basis of parental illness, might now usefully incorporate tests of putative biological markers.

SUGGESTED CROSS REFERENCES

For a discussion of genetics and psychiatry, see Section 2.1. Genetic factors in other mental disorders, such as schizophrenia, are covered in Section 15.3. For an overview of biochemical genetic factors, see Section 18.3.

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18.5 AFFECTIVE DISORDERS: CLINICAL FEATURES

HEINZ E. LEHMANN, M.D.

INTRODUCTION

Affective (mood) disorders periodically disable many people all over the world. Although manic disorders are comparatively rare, depression is, quite possibly, the most widespread, serious, and costly psychiatric disease afflicting humankind today. It is at least 10 times as prevalent as schizophrenia. Severe depression affects fully 2 to 3 percent of the world's population—some 100 million individuals—and recent studies indicate that this figure is probably an understatement. In the United States alone, some 10 to 14 million people are estimated to be afflicted by moderate or severe depression. If short-lasting (not necessarily clinically significant) forms of depression are included in the tally, possibly everyone in the world, and everybody since the beginning of time, has experienced depression.

For the 12 to 20 percent of depressed patients who are chronic sufferers, resisting any effective treatment, depression can last a lifetime. Chronically depressed individuals are among the least productive citizens and heaviest users of medical services and laboratory procedures (frequently performed to little positive avail), and thus are a major economic burden to society. Close to 30,000 people die every year in the United States alone from suicide, most of them because of depression.

Not only is depression potentially fatal in itself, but also it is a contributory and compounding factor in other terminal diseases including cancer and heart disease. The suffering associated with severe depression can be compared only with that endured by terminal cancer patients. Its "ripple effect" extends in varying degrees to family members, friends, and work associates. Living close to a depressed person can be one of the most difficult of all personal ordeals and one of the most traumatic experiences threatening infants and young children.

For every severely or moderately depressed person who has been diagnosed as such, there are many more ill who have not been diagnosed or treated. Several studies in different countries have revealed that, among healthy young adults, between 8 and 17 percent had suffered short-lasting depressive states or thoughts about suicide during the previous year—females twice as frequently as males. It is evident that even in populations that are generally viewed as "normal," depression and suicidal thoughts are widespread.

DEFINING DEPRESSION Saint Augustine commented, on the subject of time, that although everybody knows what it is, nobody can define it. With depression, it is frequently more convenient, at least for the professional clinician, to substitute "you know what I mean" for more precise formal definitions.

Depression, as a clinical entity, has no really objective, external criteria to define or diagnose it despite a prolonged and passionate search for clear biological markers in recent years. Among the keys to a true definition would be a neat dividing line between a clinical depression and the quite natural feelings of sadness, listlessness, gloom, and pessimism associated with, for example, the death of a loved one. The third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) draws one line at 2 weeks duration of key symptoms, but this period is arbitrary at best.

The question, What is depression?, elicits responses almost as varied as the orientations of the observers. A behaviorist might define depression as the defective functioning of reinforcing, conditioning mechanisms, or perhaps as the consequence of "learned helplessness" in the face of repeated failure. A neuroscientist might equate it with an intracerebral lack of balance between certain essential neurotransmitters, modulators, and hormones, or as a disturbance of neuronal receptor mechanisms. Feminists account for the higher incidence of depression in women as an outgrowth of society's subjugation of women. Others see depression as a disease arising from a cognitive disturbance leading to a negative self-concept and pessimistically distorted view of the world and future. Some psychoanalysts consider the turning inward of

aggression to an ambivalent, lost, and introjected object to be the principal feature of depression.

Semantic confusion derives from the fact that the term depression has many different meanings in different contexts, e.g. in economics, meteorology, or physiology, in addition to its behavioral connotations. Even in psychiatry, depression may refer to a symptom—such as a specific, dysphoric affect—or to a syndrome, constituted, for instance by dysphoric mood, psychomotor retardation, insomnia, lack of energy and weight loss, or to a disease, e.g. unipolar depression.

Because depression means so many different things to different people in different contexts, repeated attempts have been made to find a new name for the psychiatric illness that is termed depression. A short list of proposals includes melancholia, acedia, anhedonia, and Burton's disease. None of these names has caught on for clinical use, although one should not rule out the future possibility of such a name change in view of the substitutions that have been made for other conditions, e.g. schizophrenia for dementia precox, Alzheimer's disease for senile dementia, and Briquet's syndrome for hysteria.

As with other functional mental disorders, the causes of clinical depression are unknown. To be sure, severe environmental pressures, such as the death of a spouse, the loss of a limb, or a diagnosis of cancer, frequently precede severe depression. It cannot be said with any certainty, however, whether these stresses caused the depression, or whether they merely precipitated the depression in an already vulnerable, constitutionally predisposed individual. Questions remain: Why are some people stricken with depression, whereas others, exposed to an apparently identical array of stresses and losses, are able to cope with them? Are stresses that appear identical always equivalent? Similar-appearing stresses may have different meanings and degrees of severity for different individuals, and even when stress severity is equated, the coping ability of different individuals varies greatly.

As with schizophrenia and other major functional psychiatric disorders, two fairly distinct schools have emerged. One views the causes as environmentally conditioned, psychogenic, reactive, somatogenic, or exogenous and the other as endogenous—or, because unknown, cryptogenic. Other recently proposed terms to replace endogenous are endogenomorphic or autonomous depression, with the understanding that this type of depression is not environmentally but mainly biologically determined. At one extreme, the biologically oriented investigator holds that every depression is of "endogenous" origin—that is, biologically determined—although environmental factors may play an important role in triggering the biological mechanisms that precipitate a depressive episode. At the other extreme, the strongly dynamically oriented psychiatrists believe that every depression is psychogenic and invariably brought on by environmental or intrapersonal, conscious or unconscious, psychological stresses.

Without any doubt, tremendous strides have been made in recent years in identifying chemical and hormonal factors associated with clinical depression. There is, however, by no means final evidence that such factors are the direct cause of depression, only that they occur simultaneously with depression.

In the author's opinion, pathological depressions are the result of the loss of a person's capacity to maintain a homeostatic adjustment to the "normal" onslaught of the multiple depressing or upsetting events, or even mini-events, of every day, e.g. minor disappointments, losses, changes. Instead of normalizing, the depressed affect, after a brief depressive reaction, gets "stuck" and persists as a dysphoric mood.

Several authors have extended Freud's notion of signal anxiety to develop a signal function of depression as well. As the onset of anxiety alerts the organism to an adaptive fight-or-flight reaction, signal depression alerts a person to activate a selective filtering system that isolates the specific lost objects and sets in motion a constructive, time-limited process of working through a grief reaction to this particular loss. If this selective system fails to operate, the depressive affect that should have had a limited duration and severity overwhelms the sufferers, changing their entire perspective of the universe. *All* is lost and adaptation to a limited loss is no longer possible. The adaptive, conservative withdrawal mechanism that should have worked to save emotional energy for the grief work of normal mourning (working through) has failed and become total withdrawal without any adaptive component.

CLASSIFICATION

Perceptive physicians have long known that pathological depressions are frequently associated with apparently unmotivated states of excitement occurring in the same individuals at different times. Falret (Fig. 18.5–1) was the first to label this condition, in 1854, *folie circulaire*, the illness that today would be called a bipolar affective disorder.

Even more incisive was Kraepelin's nosological distinction, in 1896, between dementia precox and manic-depressive psychosis, even though both had been established as functional and endogenous diseases; that is, neither was associated with demonstrable physical changes in the brain nor with any situational, psychological, or social trauma that might have been thought to be the cause of the disorder.

At the beginning of this century, Freud presented his theoretical analysis of the different psychodynamics that characterize normal grief reactions (mourning) and pathological depressions (melancholia). He postulated that the normal

FIGURE 18.5–1. *Jean Pierre Falret, 1794–1870. (Courtesy of Osler Library, McGill University, Montreal.)*

working-through process of grief after a traumatic loss always succeeded in reinvesting in other available objects the libido that had originally been attached to the lost object. Patients suffering from melancholia, however, had introjected the lost libidinal objects. Thus, unable to reinvest the libido attached to it, the patients had to inflict on themselves the consequences of their anger toward the introjected, ambivalent objects, only to bring about despair, guilt, and self-destruction.

Freud's classic monograph, *Mourning and Melancholia*, is still the only source for a theoretical distinction between the essential characteristics of normal grief and pathological depression, because the phenomenology of both conditions may be identical, and as yet there is no experimental evidence of any neurochemical or neurophysiological differences between the two conditions.

FROM KRAEPELIN TO THE ERA OF ANTIDEPRESSANT THERAPY The question then arose whether as yet unknown factors of an endogenous nature or certain acute physical or psychosocial stresses or neurotic preexisting conditions or, finally, a predisposing personality structure might suggest various subgroups of depression. None of these assumed that etiologies could be defined with great precision. Nevertheless, a classification into endogenous (autonomous) depression, neurotic depression, psychogenic (reactive) depression, and depressive personality was accepted by many clinicians for the first half of the century.

Endogenous depressions were described as occurring in normal personalities without neurotic symptoms and in the absence of any time-related stresses. Neurotic depressions were diagnosed if the patient so afflicted had presented long-standing neurotic symptoms that finally seemed to converge into a clinical depression. A diagnosis of psychogenic (reactive) depression was made only if there was a close temporal relationship between major stressful circumstances and the sudden manifestations of depression in a previously well-functioning individual. Finally, the diagnosis of depressive personality was reserved for those patients who maintained a depressive, pessimistic outlook and personality structure all their lives, and in whom the depression was apparently the outcome of a permanent and continuously growing depressive disposition.

Although Kraepelin at first included neurotic and reactive depressions under the heading manic-depressive psychosis, later separating them under the label psychogenic depression, he considered the depressive personality to be an early predisposition to manic-depressive psychosis. As *typus melancholicus*, this personality disorder later received much attention in the German psychiatric literature.

Involutional melancholia, a depression occurring at the involutional age between 40 and 60 years of age, was another form of depression that Kraepelin first considered as a separate category; however, he later worked it into the framework of manic-depressive psychosis. His judgment was vindicated when, after years of great popularity as an independent diagnosis among European and American psychiatrists who had disagreed with Kraepelin, involutional melancholia was finally eliminated as a diagnosis in its own right in the official diagnostic manuals in Europe and the United States, the ninth revision of the *International Classification of Diseases* (ICD-9), and DSM-III.

Manic states have always been less differentiated than depressions. Kraepelin, however, also identified mixed states that presented a combination of manic with depressed symptoms, and this category is still accepted. Interestingly, there is not as much evidence for the occurrence of reactive manic states as there is for reactive depressions. Apparently, primary adjustment reactions to stress are most frequently comprised of tension, anxiety, aggression, and depression and very rarely, if ever, of elation, even though psychoanalytic theory regards manic euphoria as a denial defense against depression.

Many, but not all, psychiatrists agree that a specific group of symptoms points to a diagnosis of endogenous rather than neurotic/reactive depression; that is, marked diurnal variations of mood, early waking, weight loss, preoccupation with guilt, psychomotor retardation, feelings of pressure, and general lack of responsiveness. Other symptoms, such as emotional responsiveness to environmental stimuli, hysterical manifestations, and early insomnia, as well as time-related, situational stress factors, are more indicative of neurotic-reactive depressions.

The introduction of effective antidepressant pharmacotherapy in the late 1950s set off a search for new and better classifications of the depressive disorders. The tremendous amount of research that has actually developed in this field during the last two decades has exceeded most expectations.

Endogenous versus neurotic-reactive depression In recent years such sophisticated statistics as factor analysis, cluster analysis, and principal components analysis have all been widely used in statistical approaches to the problem of classifying depressive disorders. A great number of depressive subgroups have been established in this manner, not all corresponding to meaningful clinical syndromes. One result that has emerged with fair consistency from most statistical studies is the probable existence of a factor (or a group of symptoms) that closely resembles the old clinical diagnosis of endogenous depression. Most statistical analyses, however, have not demonstrated a clear bimodal distribution of depressive states and have failed to reveal the existence of a distinct neurotic-reactive factor.

Therefore, the long-standing controversy that started in the second quarter of this century, still continues: whether the traditional dichotomy between endogenous (autonomous) and reactive (neurotic) depression is justified, as many psychiatrists since Kraepelin have maintained, or whether all depressions are of one type; that is, either all endogenous, as some biologically oriented psychiatrists would believe, or all neurotic-reactive, as is assumed by some psychoanalysts. A third theory that has gained wide acceptance in recent years postulates that all depressions are distributed on a continuum between endogenous and reactive, with no depression being entirely of one type or the other (Fig. 18.5–2).

The difficulty of determining whether a given depression is caused by endogenous or environmental factors has led some investigators to propose somewhat tortured compromise classifications, such as endoreactive or endogenomorphic depression.

Primary versus secondary depression The American school of psychiatry, instrumental in conceptualizing many of the basic rules that have led to the Research Diagnostic Criteria (RDC) of psychiatric diagnoses and eventually to the system underlying the development of DSM-III, has introduced the distinction between primary and secondary depression. A primary depression, according to this school's definition, has not been preceded by and is not associated with any other psychiatric disorder, e.g. a neurosis, psychosis, or alcoholism. Secondary depression may demonstrate such an association either in the history of the patient's illness or by an examination of the patient's present condition.

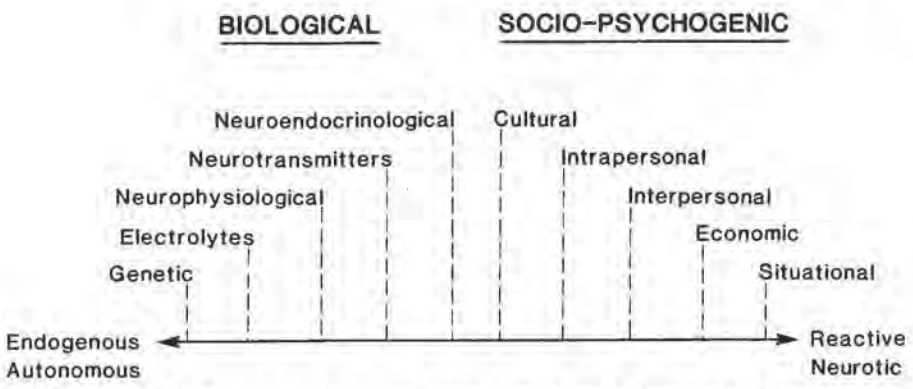

FIGURE 18.5–2. *Biological and sociopsychological factors related to classification of depression.*

Unipolar versus bipolar disorder First proposed in 1957 in Germany and confirmed independently in 1966 by Swiss and Scandinavian investigators, the distinction between unipolar and bipolar affective disorders has now been generally accepted. *Unipolar affective disorders* are clearly characterized by the exclusive presence or history of either depressive (or manic) symptoms. It has been shown that *bipolar affective disorders* tend to have an earlier onset, shorter duration of episodes and cycles, more frequent recurrences, and a higher incidence of affective disorders in patients' families. Furthermore, there is apparently an equal incidence of bipolar affective disorders in both sexes, whereas unipolar depressions occur with greater frequency in women. Unipolar depressions are at least twice as common as bipolar depressions.

More recently, the differentiation between unipolar and bipolar affective disorders has been questioned on the grounds that genetic factors suggest instead that the different manifestations of the recurrent affective disorders may simply be different phenotypic expressions of the same illness but differentiated by varying intensities of genetic loadings.

The concept of affective spectrum disorders was introduced when certain investigators observed that problems other than depressive or manic psychiatric disturbances, such as alcoholism or unstable personalities, occurred in disproportionate numbers in families of unipolar or bipolar probands. Pure and sporadic affective disorders have been distinguished according to a positive or negative family history.

New classifications of depressive states have sprung up so rapidly and in such large numbers since the 1960s that only confusion could result from reviewing all, or even most, of them in detail. For example, one group of investigators separated four different types of depression by factor analysis and denoted them simply as types *A*, *B*, *C*, and *D*. These types resembled, respectively, the retarded, anxious, hypochondriacal, and angry symptom types. Another typology distinguishes between psychotic, anxious, hostile, and depressed patients with personality disorder. Early and late onset of depression also provided characteristics for grouping depressive disorders. Still other groupings refer to special types of chronic depression; treatment-resistant depression; retarded, agitated, and dysphoric or endogenomorphic, neurotic, and reactive depressions.

The principal value of all these categorizing efforts well may lie in the potential that new emerging groupings might allow the formation of more homogeneous populations of depressed subjects on the basis of more rational and objective criteria. Such homogeneous groups, it is hoped, will then make it possible to test hypotheses about the pathophysiology of depressive disorders, and the new insights thus gained might not only satisfy scientific curiosity but also lead to more specific and effective treatments for depressed patients.

The traditional assumption, however, that similar clinical manifestations are the results of similar etiological factors, such as similar pathophysiology expressing itself in similar psychopathology, is not always warranted. It may be that behavioral manifestations are not the best indicators of different etiological or pathophysiological factors, but even if so, what other manifestations could be chosen for the demarcation of homogeneous groups of depressed patients?

CRITERIA FOR CLASSIFICATION Six different types of criteria currently used to classify depressive states are as follows:

1. Outcome, according to the natural history of the disorder (Kraepelin's original distinction between manic-depressive psychosis and dementia precox was based on this criterion);
2. Episodicity or periodicity, according to the frequency and nature of recurrent attacks, such as unipolar-bipolar disorder;
3. History of factors related to onset of the condition, such as endogenous versus reactive depression, according to the presence or absence of a time-related stress;
4. Symptoms, such as retarded or anxious depression;
5. Biological factors, such as neuroendocrine responses, level of transmitter metabolites in the cerebrospinal fluid (CSF), or genetic loading, as expressed in the family history;
6. Treatment response, for instance, to tricyclic or monoamine oxidase inhibitor (MAOI) antidepressants.

Psychotic depression Although Kraepelin always spoke and wrote of manic-depressive psychosis, today the term psychotic depression urgently calls for more rigorous semantic clarity. The term is frequently used synonymously with endogenous, in contrast to neurotic-reactive depression, or to denote simply a more severe depression. The latter usage is generally accepted in British psychiatry. If indeed psychotic symptoms are present, the adjective, psychotic, may modify the diagnosis of a depressive or manic state. Otherwise, for precision and clarity, it should not be used. Further, psychotic symptoms are not just more severe symptoms, but have the different quality of involving, in addition to affective or behavioral manifestations, cognitive and perceptual distortions, i.e. delusions, formal thought disorder, or hallucinations. Psychotic symptoms are observed in only 15 to 20 percent of severe depressions (Table 18.5–1).

TABLE 18.5–1
Diagnostic Features of Major Depressive Episode with Psychosis*

Essential Features	*Associated Features*	*Other Features†*
A. Meets criteria for major depressive episode B. Gross impairment in reality testing as expressed either in hallucinations, delusions, or depressive stupors	Hallucinations or delusions may be mood-congruent or mood-incongruent	Differential diagnosis between major depressive episode, schizoaffective disorder, or schizophrenia with depression must be considered

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.
† Not cited as a clinical feature in DSM-III, but may be present in these disorders.

Exogenous affective disorder Another type of depression that has received relatively scant attention until recently is the exogenous affective disorder for which an organic brain dysfunction is found or assumed to be an etiological factor. This type, distinguished from functional disorders, is referred to in DSM-III as organic affective syndrome. Recent studies have shown that its specific nature is often difficult to determine. Occurring more frequently in aging rather than younger people, the prognosis is less favorable than for the functional affective disorders; in fact, the disorder almost always ends in dementia. In DSM-III the diagnostic criteria are: a predominant disturbance in mood with at least two symptoms of a manic or major depressive episode, no clouding of consciousness, no dementia, and evidence from the history, physical examination, or laboratory tests of a specific organic factor that appears to be etiologically related to the disturbance (Table 18.5–2). Although men are more likely than women to be affected by this syndrome, other genetic factors do not seem to play a significant role.

TABLE 18.5–2
Diagnostic Features of Organic Affective Syndrome*

Essential Features	*Other Features†*
A. Disturbance in mood, with at least two of the symptoms listed as criteria B for manic or major depressive episode	May be difficult to distinguish from pseudodementia that is secondary to depression
B. No clouding of consciousness No significant impairment of cognitive functions No predominant delusions or hallucinations	Differential diagnosis: early manifestations of progressive brain disease, e.g. Alzheimer's disease or multi-infarct dementia
C. Clinical evidence from history, physical examination, or laboratory tests of an organic factor judged to be etiologically related to the disturbance	

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.
† Not cited as a clinical feature in DMS-III, but may be present in these disorders.

Depressive equivalents Certain psychiatric conditions that may occur as symptoms of a depressive syndrome, but were never before categorized as depressions per se, have, somewhat unexpectedly, been found to respond to antidepressant pharmacotherapy. It has therefore been suggested that these conditions may be depressive equivalents or variants. These disorders are recurrent spontaneous panic attacks, agoraphobia, obsessive-compulsive disorder, and chronic pain. From the methodological point of view, it is doubtful whether these disorders belong to the same nosological sphere as depression solely because the conditions frequently respond to the same treatment as depressions.

Others have suggested that alcoholism and other addictive disorders, even delinquent acting-out behavior, may sometimes be depressive equivalents, not because they respond to antidepressant treatment but because of the complex and ambiguous, dynamic interactions between some of these disorders and depression.

TABLE 18.5–3
Diagnostic Table of DSM-III Categories of Affective Disorders

	Organic brain syndrome
293.83	Organic affective syndrome
	Bipolar affective disorder
296.6x	mixed
296.4x	manic
296.5x	depressed
	Major depression
296.2x	single episode
296.3x	recurrent
	Atypical affective disorders
296.70	Atypical bipolar disorder
296.82	Atypical depression
	Other specific affective disorders
300.40	Dysthymic disorder (depressive neurosis)
301.13	Cyclothymic disorder
	Adjustment disorder
309.00	with depressed mood
309.28	with mixed emotional features
309.40	with mixed disturbance of emotions and conduct

DSM-III and ICD-9 Two major systems of classification have been officially adopted in most countries to standardize all psychiatric diagnoses: the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) in the United States and the ninth revision of the *International Classification of Diseases* (ICD-9). Tables 18.5–3 and 18.5–4 represent extracts of those listings in each system that refer to the affective disorders. (Operational and other diagnostic criteria for many of these conditions are given later in more detail under the subheading "Differential Diagnosis.")

Such composite comparative listing of various names and numbers, applied to affective disorders in the two systems, might not only be a reminder of the richness of the current conceptualizations of affective disorders, but it may also underline the still broadening confusion in the classification of these disorders. There is good reason, however, to expect that a fuller integration of the two systems will soon be achieved.

At this writing not all of the numbers in the two systems correspond to each other. Some items are easier to equate than others when the diagnoses carry different names, e.g. manic-depressive psychosis in ICD-9 becomes bipolar affective disorder in DSM-III. The continuation of a traditional name in the former fails to take into account that many depressive episodes of manic-depressive patients are clearly not of a psychotic nature and should not be so diagnosed.

TABLE 18.5–4
Diagnostic Table of ICD-9 Categories of Affective Disorders

296	**Affective psychoses**	
296.0	Manic-depressive psychosis	—manic type
296.1	Manic-depressive psychosis	—depressed type
296.2	Manic-depressive psychosis	—circular type but currently manic
296.3	Manic-depressive psychosis	—circular type but currently depressed
296.4	Manic-depressive psychosis	—circular type mixed
296.5	Manic-depressive psychosis	—circular type, current condition not specified
296.6	Manic-depressive psychosis	—other and unspecified
296.8	Affective psychosis	—other (i.e. with information but not manic depressive)
296.9	Affective psychosis	—unspecified (i.e. insufficient information to specify)
298	**Other nonorganic psychoses (reactive to recent experience)**	
298.0	Depressive type (resembling manic-depressive, depressed type)	
298.1	Excitative type (resembling manic-depressive, manic type)	
300	**Neurotic disorders**	
300.4	Neurotic depression	
301	**Personality disorders**	
301.1	Affective	
308	**Acute reaction to stress**	
308.0	Predominant disturbance of emotions (includes depression)	
308.4	Mixed reaction (depressed can be a minor component)	
309	**Adjustment reaction**	
309.0	Brief depressive reaction	
309.1	Prolonged depressive reaction	
309.3	With predominant disturbance of conduct (can include depression as a minor component)	
309.4	With mixed disturbance of emotions and conduct	
311	**Depressive disorder, not elsewhere classified**	
311.9		
312	**Disturbance of conduct not elsewhere classified**	
312.3	Mixed disturbance of conduct and emotions (includes misery)	
313	**Disturbance of emotions specific to childhood and adolescence**	
313.1	With misery and unhappiness	

TABLE 18.5–5
Diagnostic Features: Adjustment Disorder*

Essential Features	*Associated Features*
A. Maladaptive reaction to recognized psychosocial stressor occurring within 3 months of onset of stressor	Duration may be brief or long, depending on the stressor and level of adaptation
B. Maladaptive nature of reaction indicated by either: 1. Impairment in social or occupational functioning; or 2. Symptoms in excess of an expectable reaction to the stressor	Personality disorder or organic mental disorder may render individuals more vulnerable to adjustment disorder
C. Disturbance not merely one instance of overreaction to stress or exacerbation of other mental disorder	
D. It is assumed that the disorder will remit after the stressor ceases or with a new level of adaptation	
E. The disturbance does not meet criteria for other specific disorder or for uncomplicated bereavement	

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3, American Psychiatric Association, Washington, DC, 1980.

In DSM-III, neurotic depression does not appear, and the term "neurosis" is avoided as much as possible. Brief and prolonged depressive reactions in ICD-9 are called adjustment disorders with depressed mood in DSM-III (Table 18.5–5). Reactive depressive and manic psychoses of ICD-9 are not represented in DSM-III where they would probably be equated with atypical psychosis. Organic affective syndrome of DSM-III has no corresponding listing in ICD-9.

Neither ICD-9 nor DSM-III use the long-popular term "involutional melancholia," a category that has now been incorporated into manic-depressive or major depressive episode disorder (Table 18.5–6).

To date, there is no closure on the proliferation of categories of the affective disorders. These important changes, however, have clearly emerged during the last 10 years: (1) the final abandonment of the diagnostic concept of involutional melancholia; (2) the introduction of the unipolar-bipolar distinction; (3) the statistical confirmation of a symptom cluster that is characteristic of the old endogenous type; and (4) the discoveries of biological factors that may, in the not-so-distant future, be objective criteria for the classification of depressive disorders and also hold promise for the establishment of more rational and specific indications for their treatment.

PHENOMENOLOGY

DEPRESSIVE STATES In simplest terms, depressive states typically show a combination of three psychological symptoms: (1) depressed mood (feelings of hopelessness, guilt, worthlessness, psychic pain); (2) drive inhibition (loss of energy); and (3) anxiety. These psychological symptoms are associated with certain functional symptoms usually including disturbances of appetite, sleep, and sexual libido. Behavioral symptoms, such as social withdrawal, crying spells, and suicidal behavior, occur along with the typical depressive posture and facies with furrowed brow, turned-down corners of the mouth, and lack of animation (Figs. 18.5–3 and 18.5–4). The depressed patient typically becomes (1) less productive than usual, (2) less capable of enjoying life, and (3) less able to become interested in, or form attachments to, people, causes, or things. These changes persist over an inappropriately prolonged period of time.

Various observers have reported literally hundreds of specific depression symptoms that are interspersed in the three major categories of symptoms listed above. The list ranges from listlessness and disabling backache to infanticide. Several studies have shown that, in retrospect, lack of energy, fatigue, and insomnia have usually been the first symptoms of a clinical depression, followed within a few days or weeks by the core symptom of the depressed mood. This sustained, fixed mood of feeling sad, gloomy, blue, despairing, and pessimistic, with a restricted range of emotional response that makes smiling difficult or impossible, is by far the most frequent symptom of all clinical depressions. It may not, however, be prominent in every case or may be overshadowed by other symptoms, such as in masked depressions.

Frequently, the kind of depressed affect that characterizes the severely depressed mood is difficult to describe, because it has a distinct quality that is hard to appreciate for those, including professionals, who have not experienced it.

The distinct quality of affect in melancholia Poets and philosophers have, through the centuries, attempted to define this special quality of inconceivable isolation and despair.

Shakespeare's Hamlet, perhaps the melancholic prototype, said, "I have of late—but wherefore I know not—lost all my mirth, foregone all custom of exercises, and indeed it goes so heavily with my disposition that this goodly frame, the earth, seems to me a sterile promontory; this most excellent canopy, the air, look you, this brave o'erhanging firmament, this majestical roof fretted with golden fire—why, it appears no other thing to me but a foul and pestilent congregation of vapors."

The nadir of Dante's *Inferno* was actually a frozen sea of ice in which inhabitants were immobilized for an eternity.

TABLE 18.5–6
Diagnostic Features of Major Depressive Episode*

Essential Features	*Associated Features*	*Other Features†*
A. Persistent dysphoric mood: depressed; low; irritable; hopeless Loss of interest Loss of pleasure	Symptoms usually develop over days or weeks, but may appear suddenly	Lack of animation in facial expression and voice
B. At least 4 of these symptoms for at least 2 weeks: 1. Poor appetite or weight loss or increased appetite or weight gain 2. Insomnia or hypersomnia 3. Psychomotor agitation or retardation 4. Loss of interest in normal activities or decrease in sexual drive 5. Loss of energy 6. Feelings of worthlessness, inadequacy, or excessive (inappropriate) guilt 7. Reduced concentration or indecisiveness 8. Suicidal ideation	Difficulty in starting any activity, sometimes even simple self-care Over 50 percent will have recurrent depressive episode Individuals with recurrent depressive episodes are at greater risk of developing bipolar disorder Functioning between episodes usually returns to premorbid level In 20 to 30 percent the course is chronic with residual morbidity and social impairment	Marked poverty of ideas Self-centered; unable to care for others Often increased irritability Social withdrawal Regressive dependence on others
C. No preoccupation with mood-incongruent delusions or hallucinations		
D. Not superimposed on schizophrenia, schizophreniform, or paranoid disorder		
E. Not due to organic mental disorder or bereavement		

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.
† Not cited as a clinical feature in DSM-III, but may be present in these disorders.

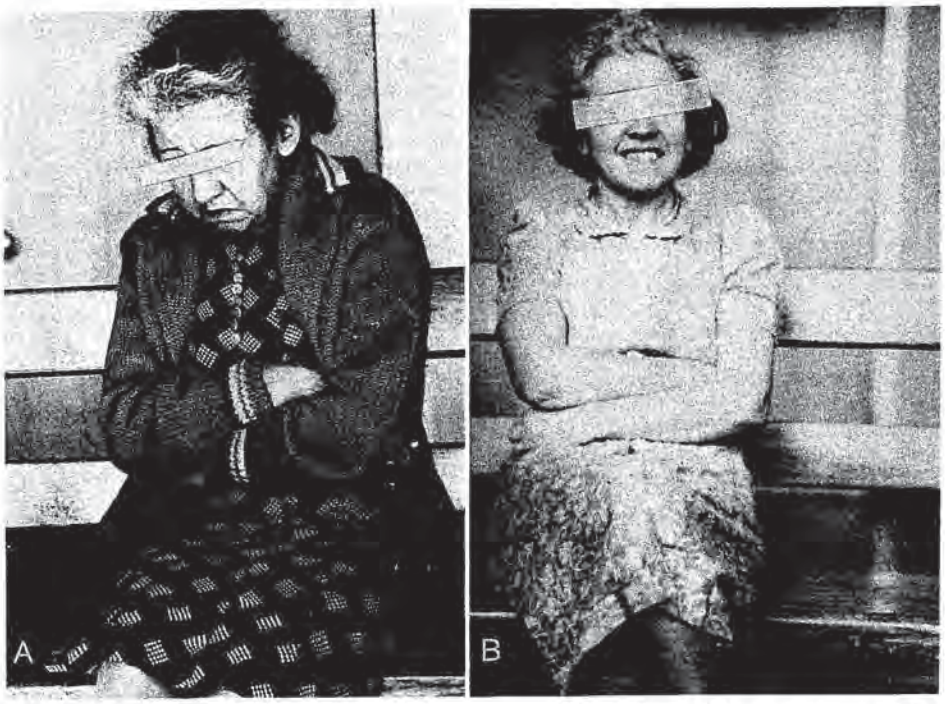

FIGURE 18.5–3. *A 38-year-old woman during a state of deep retarded depression* (A) *and 2 months later, after recovery* (B). *Note the turned-down corners of the mouth, the stooped posture, the drab clothing, and the hairdo during the depressed episode. (Courtesy of Heinz E Lehmann.)*

For Kierkegaard, who believed that despair is entwined with man's eternality, even death was not an escape. This philosopher commented, " . . . to be sick until death is not to be able to die . . . . Even the last hope, death, is not available."

Existential aspects It is generally agreed that anxious patients are oriented toward the future and that manic patients live in the present. Depressed persons, however, are imprisoned in the past and cannot experience any real present. Also they have no future and have lost all potential to develop, to become. Their sense of time is actually disturbed, and they experience time as passing much slower than they would in a nondepressed state. With all this they have lost the concept of reality and self-identity.

Persons who are deeply depressed cannot feel the sadness that they used to be capable of feeling. Ordinary sadness, which can be shared with others and thus made easier to bear, is the psychic pain experienced by someone who has been hurt by an event or a person, either of which remains prom-

FIGURE 18.5–4. *The Swiss neuropsychiatrist Veraguth has described a peculiar triangle-shaped fold in the nasal corner of the upper eyelid (arrow). This fold is often associated with depression and referred to as Veraguth's fold. The photograph illustrates this physiognomic feature in a 50-year-old man during a major depressive episode. Veraguth's fold may also be seen in individuals who are not clinically depressed, usually while they are harboring a mild depressive affect. Electromyographically, it has been shown that distinct changes in the tone of the corrugator and zygomatic facial muscles accompany depression. (Courtesy of Heinz E Lehmann.)*

inent in the mind and full of meaning even if a physical loss is involved. Pathologically depressed persons, however, view the world as remote and empty or cluttered and utterly without meaning or potential (Fig. 18.5–5).

Although feeling an intolerable oppression, these persons tend to be incapable of normal grief or of feeling normal concern. One severely depressed patient wrote:

> I have felt sad, but what I have found the most awful is the feeling of not caring for my wife, my two daughters and my 5-year-old boy (a kind of emotional anesthesia). I feel worthless and I feel passé. I do not believe what is written about me in letters of reference. I feel I will not be up to it and will make mistakes. I think every day about the mistakes I have made and about the hard times my wife has had. I ask myself questions about my future which I see as gloomy; I see little hope for me and cannot see how I can improve things.

For the severely depressed patients, incarcerated in the past, incapable of loving or being reassured, and often harboring heavy guilt feelings, there is no present or future in which to undo the factors contributing to that guilt. They are condemned to hopelessness because they have no new chances ever to atone or compensate for any of those acts and omissions of the past for which they must, as does everyone, have grounds to feel guilty.

Diurnal variations In many depressed patients, most frequently those of the so-called endogenous type, there is a distinct difference in mood between morning and evening, with mornings being the most depressive time of the day and improvement occurring toward evening when patients can look forward to relief from misery through sleep. Patients with atypical depressions, in whom environmental factors may have played an important role in precipitating depressive episodes, and who are capable of reacting to efforts to cheer them up, often feel worse in the evening than in the morning.

Anxiety Virtually all depressed patients suffer from anxiety, although the reverse is not necessarily true. Anxiety has an arousal function, whereas depression inhibits. In most depressions, these two states exist together, albeit with contradictory functions and in opposite directions.

FIGURE 18.5–5. *"Melancholia" by Albrecht Dürer, 1471–1528, showing a winged figure in the typical depressive posture surrounded by scattered rubble of a meaningless world.*

Agitation and retardation In agitated depressions, the anxiety

component is dominant and spurs the patient to repetitive, aimless restlessness manifested in endless pacing, hand-wringing, and moaning.

In retarded depressions, the inhibiting component prevails over the arousal component; the patient is very slow-moving, speaks in a low, toneless voice, and shows greatly reduced energy. In extreme cases, the patient may remain motionless, stony-faced, in a stooped posture, or may even be mute, in a depressive stupor.

In both types, the poverty of ideas is striking. Agitated patients may feel compelled to repeat over and over the few ideas they have, whereas retarded patients may be incapable of expressing even the content of their stereotyped ruminations.

Retardation is more frequently observed in younger patients, whereas agitation is more common in older ones. A young person with recurrent depressions may exhibit retarded depressions until age 40 or 50 at which time the pattern may change to agitated episodes.

Guilt feelings Feelings of guilt, which have long been thought to be characteristic of an endogenous depression, are no longer considered an essential factor in diagnosis. Feelings of personal inadequacy seem to have replaced guilt feelings. One trend that probably has contributed to this shift has been the loosening of religious value structures in society.

One middle-aged accountant, suffering from a major psychotic depression, recently reported severe guilt feelings because he had engaged in masturbation—the last time fully 6 months before the interview. This anachronistic attitude came as a surprise to the author.

Low self-esteem is characteristic of most depressed patients. Some theoreticians consider it the hallmark of all pathological depressions. Their reasoning is that loss of self-respect, self-confidence, and self-esteem reflect a fundamental cognitive disturbance that changes the depressed person's self-concept and perspective of the world radically and negatively. In actual clinical practice, however, it is not unusual to see severely depressed patients whose self-esteem is relatively intact; instead, their main pathological focus is on an important loss that they have sustained.

Indecision One of the most painful symptoms suffered by depressed patients is their incapacity to make decisions, even of a minor sort.

On awakening, should the patient stay in bed or get up? Shave or not? Which shirt should be put on? A tie or no tie? What should breakfast be? This pattern of indecision persists through all waking hours. As one patient, a professional, put it: "It came to a point where I did not trust my judgment even in the smallest things and would freeze rather than act."

It may be difficult, even for the trained clinician, to appreciate the painful process that most depressed people often go through in attempting to make such minor decisions, not to mention the many larger decisions that confront everyone daily.

Fatigue Lack of energy, caused by the inhibition associated with every depressive disorder, leads to another particularly troublesome symptom: continuous fatigue. At its extreme, this lack is responsible for the very low energy output of the severely depressed and retarded patient who seldom moves and may speak in almost inaudible monotones. More frequently, the low energy levels result only in constant fatigue that makes planning or taking any action almost impossible. There is no initiative and no strength and, as a result, no self-confidence.

One patient noticed that, a week or two before the onset of a depressive episode, he had an unusual disinclination to talk. He also noticed that, during the early phases of his depressions, when he was still functioning, he did not like to initiate any action, to the point of not wanting to see a taxi ride or plane ride end because that would mean that he had to take some initiative again.

A second patient described it this way:

One of the worst symptoms is fatigue. It occurred for the first time 2 years ago. I was playing golf with friends. On the 10th hole, I felt like I felt at the end of a 3-mile race when, years ago, I was running for the Army. The fatigue I felt was very similar to physical fatigue. I generally feel fatigue at first when waking up, but I cannot fall back asleep. A few minutes later I have to get up because of the brooding; getting up is painful but I feel forced to do it.

A third patient wrote this description of her feelings:

In early November, I woke one morning and looked out the window, and all I could see was a long black road. It seemed to stretch as far as I could see. From then on till the end of January I became a completely different person. It was as if a monster took over my life. I had no energy, no motivation. I did not get dressed, just wandered around the house all the time doing nothing, did not care about myself or anybody else, did not even attend to my own personal hygiene. I commenced to drink and no matter how much I drank I never became intoxicated.

Loss of memory is a typical complaint of depressed patients; however, if they are specifically tested, the clinician frequently finds that this subjective complaint has little or no objective substrate.

Lack of concentration is a very common symptom of depression. Its severity may range from reduced productivity at work or lessening of the richness of ideas to inability to read a newspaper or follow a television program. This is also one of the last symptoms to fully disappear during recovery from a major depressive episode.

A depressed university teacher described it this way:

I often have to read paragraphs over and over. I have problems following conversations. My ability to write has been nil. My last publication was 4 years ago (but written before then). I cannot complete some 7 scientific manuscripts. Except for the discussion, these manuscripts were completed 4 years ago. I do not have the interest, the energy or the confidence to finish them.

In another instance a psychiatrist, himself subject to recurrent depressions, reported that the first symptom of his depressions was loss of sexual drive, followed shortly by failing concentration, which resulted in a disinclination to read even the newspaper, before a full-blown depression set in. These were also the last symptoms to disappear after he recovered.

Loss of appetite, leading to substantial weight loss, is another typical symptom in the endogenous or autonomous (biologically determined) type of depression. Many depressed persons are not capable of enjoying formerly favorite foods. They may have to force themselves to eat even the greatest delicacies, which now seem tasteless.

A minority of patients, mainly those with atypical depressions, overeat and may gain weight, and that symptom may further depress some already depressed women.

Constipation is very common among depressed patients, often aggravated by antidepressant drugs prescribed for them. Many patients seem to put excessive emphasis on the inability to evacuate their bowels properly.

Loss of sexual drive is an almost universal symptom in depressed persons. For men, there is usually a history of little or no libido and sexual activity; for women, such activity may continue, although without interest.

Hypochondriasis accompanies depression in about 25 percent of cases. This symptom is more common among the aged depressives, and when it is present as a main complaint, it is usually very difficult to treat. A high proportion of treatment-resistant patients is found in this group.

Complaints of pain, frequently of the chronic type, are common in depression. The pain is usually located in the head, but may be in the chest or abdomen. Chronic pain in the shoulder or back also may appear as a stubborn somatizing symptom.

Obsessional, repetitive thoughts, ruminative worrying, or phobias may appear as new symptoms during a depression or, more frequently, may become pathologically compelling in some persons whose obsessional personality type predisposed them to this symptomatology even before they became depressed.

Irritability is often observed in depressed patients and is one of the features that, in combination with passivity, great dependence on others, and egocentric insensitivity, handicaps their interpersonal relationships and makes it difficult to live close to a depressed person.

Sleep disorder Sleep may offer the only daily relief for many depressed patients. Disturbances of sleep, however, are universal among these patients—insomnia occurring in about 90 percent—and are usually among the first symptoms to be reported. The anxiety pattern of insomnia is frequent, in which the patient cannot fall asleep for hours (increased sleep latency). In the depressive pattern of insomnia, early awakening (e.g. at 2 or 3 A.M.) is the rule. The remaining hours of the night are usually filled with painful ruminations. Although this last pattern is believed to be specific for depression, it is not as common as is often assumed. Most frequently, one encounters a pattern of restless, intermittent sleep: The patient can fall asleep quickly, but wakes up frequently during the night and does not feel rested in the morning.

Hypersomnia, or unduly, but mercifully, prolonged sleep (14 to 15 hours a day), afflicts a significant minority of depressed patients, particularly those suffering from atypical depressions.

Hopelessness The degree of hopelessness felt by a depressed patient is a vitally important gauge of the severity of depression and the immediate risk of suicide. A depressed patient, unconvinced of recovery or the possibility of a future, is probably delusional and thus in a psychotic state. Furthermore, subjectively, suicide would be the only "logical" resolution. Such a patient should be hospitalized immediately and monitored around the clock. Lesser degrees of a hopeless attitude, however, require careful monitoring as well.

Suicide Approximately 30,000 persons commit suicide every year in the United States alone. It has been estimated that only about 5 percent of all completed suicides are for rational, nondepressive reasons and that at least 40 to 50 percent of all suicides are committed by patients suffering from major depressions.

Suicidal thoughts are present in most, if not all, moderately to severely depressed patients, probably in at least 70 percent of them. The danger of suicide must always be considered to be present in virtually every depressed patient—if not today, then perhaps tomorrow or next week. Suicide risk is greatest among those patients who express more or less complete hopelessness.

Particularly dangerous periods are in the early stages of depression, before help has become available and while the patient is in a state of great anxiety over what is happening. Another especially dangerous period is when a patient is close to remission, has improved, and actually seems to be free of symptoms much of the time. Typically, such a patient may experience an unexpected, albeit brief, relapse in the midst of recovery, is frightened by it, and becomes convinced that the situation is indeed hopeless. Unlike in the depths of depression, strength and initiative are renewed to plan and execute a "successful" suicide. This is a point at which clinicians, family, and friends may have let their guard down. The time of release from active treatment and the following 3 months are particularly important times for all who are concerned to keep their guard up.

Women make far more suicidal attempts (parasuicides) than men, whereas men complete suicide more frequently than women.

Risk factors for suicide Although patients considered at risk for suicide are no longer scrupulously stripped of any possibly life-threatening implements, including towels and belts, and utterly deprived of privacy, *all* such patients must still be closely monitored around the clock.

In the absence of objective criteria to judge the possibility of suicide, every patient should be explicitly questioned about suicidal thoughts and plans. Those considered at very high risk are depressed patients who are constantly and compulsively preoccupied with suicide and who have made specific plans on how to carry it out.

Single, depressed men over the age of 60, living alone, with drinking problems and without religious affiliation, are at greatest risk, particularly when they show high levels of tension, anxiety, and agitation, as well as persistent insomnia. Any person with a history of previous suicide attempts also should be considered at increased risk. Other risk factors cited by recent investigators include (1) a longer current episode of depressive illness, (2) being on hypnotic drugs for more than 1 year, (3) displaying psychomotor retardation and self-neglect, and (4) making suicidal communications.

Clinicians also know that depressed patients who suddenly appear to be unusually calm may have reached the stage of firm resolution to commit suicide and should be observed with special care.

Note that all suicidal attempts—even if not clearly classifiable as attempts with lethal intent—should be taken seriously, even in nondepressed patients. Too many cases are on record in which a suicide attempt, with the patient fully anticipating being rescued, misfired when the rescuer did not arrive on time.

Extended suicide Although violence is rare among depressed patients, extended suicide has to be considered as a definite risk. Typically, a depressed mother may kill her infant(s) who are still young enough to be felt by her as a symbiotic part of herself. In one case a happily married man who was suffering from recurrent depressive episodes brutally killed his wife by pushing his fist into her mouth until she suffocated, intending to kill himself next. This unusual homicide was, in fact, a variation of the extended suicide.

Psychotic depressions In the past, significant numbers of depressed people were psychotic, expressing delusions of poverty, guilt, or nihilistic ideas, such as having no heart or no intestines or the world coming to an end. Their case histories used to fill the older textbooks. Today, one meets fewer psychotic depressed patients, because their condition is frequently diagnosed and treated by primary physicians and psychiatrists much earlier than in the past and thus held to a less severe level. Nevertheless, 15 to 20 percent of severely depressed patients still fall into the category of psychotic depression because their symptoms include hallucinations,

delusions, thought disorder, or grossly inappropriate behavior (Table 18.5–1).

Vital depression In 1920 the German psychiatrist Kurt Schneider coined the term "vital depression" to describe the loss of primary, vital energy and those biological functions that usually follow a normal daily rhythm, e.g. appetite, sex, and sleep. He also noted the appearance of tormenting feelings of pressure in the chest or head. He considered vital depression to be an essential component of an endogenous depression and one that is not primarily associated with environmental stresses. Vital depression was, until recently, a term used almost exclusively by European psychiatrists, but has now been adopted also by American clinicians as characteristic of endogenous depression. In DSM-III the diagnosis of melancholia corresponds most closely to vital depression.

Masked depressions are depressive states in which dysphoria is overshadowed or masked by obvious somatic symptoms, such as gastrointestinal problems, chronic pain, or other psychiatric disorders, e.g. drug or alcohol abuse. In elderly patients, physicians often miss the fact that depression is the most urgent pathological condition if camouflaged by hypertension, cardiac arrhythmias, emphysema, or diabetes or if manifested in an array of hypochondriacal complaints about urinary frequency, dizziness, disturbed bowel functions, or backache.

Diagnosis of masked depression is quite common in the United States and elsewhere. One survey of European general practitioners indicated that masked depressions represent 10 percent of all depressive conditions.

Atypical depression There are depressive conditions that do not fall easily into any of the diagnostic categories outlined in DSM-III or ICD-9. Some of these are depressive states that are of such short duration that many clinicians are never consulted about them, even though they may cause considerable suffering and be temporarily disabling.

Such brief depressions have been described previously in the foreign literature; in Germany they are called *untergrund-depressionen* or "underground depressions." Such depressions have more recently been studied by American authors who have determined that these abortive depressions occur most frequently among the elderly, especially those who are inactive and have some physical disease. One study found that among U.S. air traffic controllers who were still working full time at their responsible task, 0.2 percent were scoring on the Zung Depression Scale as severely depressed and close to 10 percent as moderately depressed, but definitely in the pathological range. The reason that these people did not stop working or seek professional help was that their depressions lasted less than 1 week. Such short-lasting micro-depressions are as yet a relatively uncharted area with very little known about their causes, their general epidemiological distribution, prevention, and therapy.

Because it has been repeatedly reported that atypical depressions respond better to pharmacotherapy with monoamine oxidase inhibitors (MAOI's) than with tricyclic antidepressants, recent studies have aimed at verifying these claims under controlled conditions and have offered another working definition. Atypical depressions manifest prominent symptoms of anxiety or hysteria; excessive sleep (hypersomnia); excessive eating (hyperphagia, bulimia); and mood responsiveness (the patient may be temporarily cheered by pleasant environmental stimuli).

Other depression-like states There are several types of depressive conditions that should not be treated clinically with antidepressants, and some of these are described below.

GRIEF OR MOURNING Grief is the normal reaction to a loss, whether of a person, object, or state, e.g. health, prestige, self-esteem. Such a reaction calls for sympathy and reassurance, but not for medical therapy. If a sudden, overwhelming loss leads to excessive tension, sleep loss, or agitation, tranquilizers or hypnotic drugs may sometimes be indicated but only for brief, symptomatic treatment. Physicians who prescribe specific antidepressants for a grief reaction may, at best, be wasting their efforts or, at worst, harmfully interfering with the necessary and natural process of working through the mourning period.

ACUTE DEPRESSIVE CRISES Situational crises sometimes present as acute emergencies with serious suicidal danger. Such crises often occur when a person is suddenly overcome by massive guilt or shame, e.g. unexpected jailing or accidental killing. This type of depression is acute and dangerous—but brief. One author who studied suicides and suicide attempts in prisons found that, virtually without exception, a person who made a serious but abortive suicide attempt after an arrest was in a different frame of mind the next day and happy to be alive. Antidepressant drugs are not indicated for this kind of patient; by the time they would take effect, the patient has usually recovered from the depressive state. Instead, therapeutic management should be on an emergency or crisis basis: immediate sedation and psychotherapy and continuous observation for at least 48 hours, the period during which the risk of impulsive suicide is greatest.

STRESS DYSPHORIA A question that, increasingly, plagues psychiatrists is: Does the patient who has come for treatment of what is clearly a dysphoric state suffer from a really pathological condition, e.g. depression, or is there just distress for quite understandable reasons because of, for example, job loss, separation from a spouse, serious financial problems, or because of some other problems with which the patient is struggling to cope? If the latter is the case, the symptom of worry may be a normal stress response, and far from being sick, the distress may actually have adaptive value.

Any persistent stress or long-standing disabling condition may eventually become intolerable and lead to a chronic depressed state that is characterized by exhaustion and demoralization, a state resembling the condition that is today in popular language often referred to as "burnout." This type of disorder usually calls for major psychosocial interventions, as well as other forms of treatment.

EXISTENTIAL MALCONTENTEDNESS Some patients may not even have any special coping problems, but have simply decided that they do not feel as happy as they think they have a right to feel. They insist on being treated because they do not dwell in a continuous "high" as, in their perception, is prescribed by much of popular literature today. Such persons might be classified as being existentially malcontent. Clearly, they are not candidates for antidepressive therapy.

MANIC STATES Manic episodes occur less frequently than depressive episodes and are less readily recognized as an ailment than are depressions. In the early stages of such episodes, which are classified as hypomanic, patients actually feel better than normal and often appear brighter, even younger than their age, and more energetic than usual, even to close family members and initially to medical generalists.

The manic state is a syndrome that is often viewed as the

TABLE 18.5–7
Diagnostic Features of Manic Episode*

Essential Features	*Associated Features*
A. Periods of elevated, elated, expansive, or irritable mood This mood is predominant although it may be interrupted by depressive mood	Lability of mood, often with rapid, brief shifts to anger or depression
	Increased sociability
B. Hospitalization—or duration of at least 1 week—with at least three of these symptoms, or four, if the mood is irritable: 1. Increased activity or restlessness 2. Pressure of speech or increased talkativeness 3. Flight of ideas 4. Inflated self-esteem (grandiosity) 5. Reduced sleep 6. Distractibility, i.e. reacting to many, often irrelevant, stimuli of the environment 7. High risk-taking and poor judgment, e.g. reckless driving, buying sprees, sexual indiscretions	Intrusive, demanding, tactless behavior Flamboyant dress; excessive makeup Giving away candy, belongings, money to strangers Speech rapid, loud, often filled with jokes, puns, or rhymes Occasionally loosening of associations and incoherence, even to the point of disorientation and confusion, particularly when exhausted or on medication
C. No mood-incongruent delusions or hallucinations, and no bizarre behavior if the affective syndrome (A and B) is not present	
D. Not associated with schizophrenia, schizophreniform disorder, or paranoid disorder	
E. Not due to organic or toxic mental disorder	

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.

opposite of depression. The term "manic" should be used only in the sense of a syndrome, never to denote a single symptom. The classic triad of manic symptoms consists of euphoria, psychomotor excitement, and flight of ideas, contrasting with the depressive triad of symptoms of sadness (dysphoria), psychomotor retardation, and cognitive inhibition or poverty of ideas. This is, however, an oversimplified view. Underlying the manic's elation there may be considerable anxiety and other dysphoria, e.g. irritability, although it is often difficult to recognize (Table 18.5–7).

Some manic-like depressive episodes are, in fact, mixed states. Manic behavior may be interrupted or accompanied by some depressive features, just as some depressive behavior may be characterized by psychomotor agitation not of the aimless hand-wringing type but resembling instead the manic flightiness.

Disturbed (usually reduced) sleep is virtually always common to both manic and depressive states. Although the depressed patient may complain about it, the manic patient may not feel at any disadvantage from sleeplessness. The latter simply feels a need for only 2 or 3 hours of sleep a night and therefore has the advantage of plenty of waking time to engage in any pleasurable activity.

Another symptom frequently common to both manic and depressive states is weight loss.

In the early stages of the manic state, the hypomanic individual may actually function better and be more productive than usual; in fact, some writers, musicians, scientists, and others have made valuable creative contributions during such periods. In the later stages of severe manic conditions, as in severe depressive conditions, the patients become unable to function. Although the great risk among depressive patients is personal neglect and suicide, the great dangers to a manic are the consequences of recklessness; for instance, car accidents, major losses from imprudent business gambles, and scandals ensuing from the manic's characteristic hypersexuality.

The typical image of the manic is that of a person who is "high," e.g. outgoing, overly alert, overly self-confident, frequently dressing flamboyantly and using excessive makeup, optimistic to a pathological extreme, even turning a tragedy into a positive event.

One manic-depressive woman whose son was killed along with his two friends in an auto accident became manic, instead of more typically depressed, as a reaction to this catastrophe. In her excited state she was teaching hospital patients new dance steps in the wake of her loss, and proclaiming that she was happy her son was killed, rather than have to live with guilt feelings about the death of his friends.

Such patients are playful—punning, rhyming, joking, laughing, teasing. For the careful clinical interviewer, the mere frequency of such words as play, act, dance, run, game, and fun in a psychiatric patient's speech could point toward a diagnosis of a manic state (Fig. 18.5–6).

Traditional textbooks have described misidentification, e.g. calling a person well known to the patient by a wrong name, as a symptom of manic states, ascribing it to a perceptual disorder. In most cases, however, the clinician can demonstrate by persistent questioning that the apparent misidentification actually is an expression of an overactive, playful imagination, rather than a primary faulty perception—much like children who pretend that people have an identity other than the accepted one.

Not all manic patients fit into this picture of elation. They may present, instead, an unstable, irritable, angry, or aggressive mood, but even when angry, manic patients rarely become physically violent. What is common to all these moods is their outgoing expansiveness in contrast to the withdrawn inhibition of the depressed person (Fig. 18.5–7).

Manic patients are always talking (pressure of speech) and moving. Although the talk and motion are not aimless, they are hardly ever completed or concluded to achieve worthwhile results. Overactive manic patients can be—and often are—a garrulous, loud, constantly irritating, intrusive nuisance to those around them. Because they usually leave everything

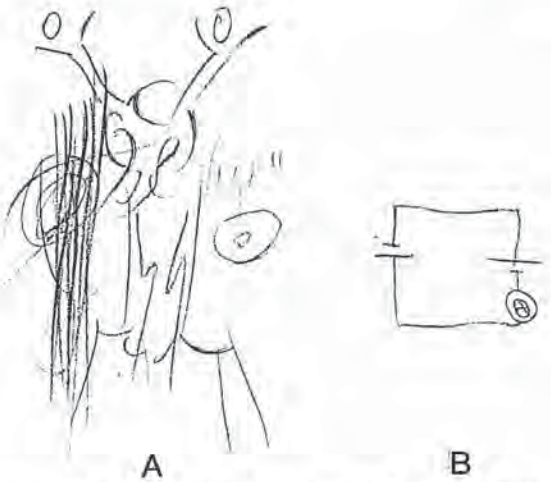

FIGURE 18.5–6. *A 22-year-old engineering student, during an acute manic episode, was asked to "draw something" and drew* A. *He commented on it: "The female system—Hi, man! See the hymen? The egg—the yolk—that's no joke!" Six weeks later, when recovering from a hypomanic state, he drew* B *and said it was "a self-charging circuit." (Courtesy of Heinz E Lehmann.)*

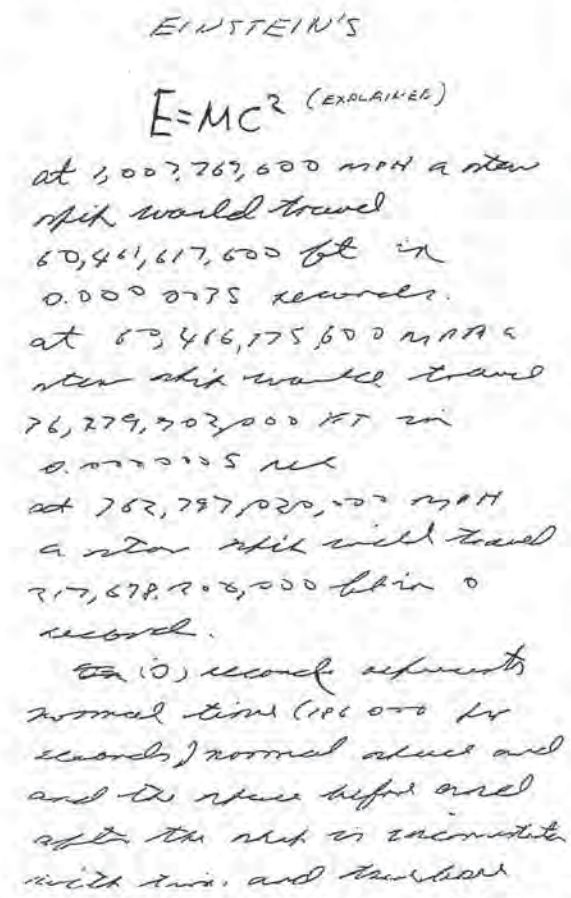

FIGURE 18.5–7. *Expansive writing from a manuscript by an airport baggage handler who attempted to "explain Einstein's $E = mc^2$" during a manic episode. (Courtesy of M Amin, MD, Montreal.)*

around them in disarray, they may be referred to as "messy manics."

Manic patients are very distractible and find it almost impossible to concentrate because their attention span is extremely short. Virtually at the mercy of the stimuli in their environment, everything they can see, hear, or touch attracts their attention and elicits their response, which, more often than not, is trivial or irrelevant.

The cognitive functioning of the manic patient is characterized by an unrestrained and accelerated flow of ideas. This flight of ideas must be distinguished from normal individuals' perhaps circumstantial digressions from a point they want to make and to which they eventually return in discussion. It also should be differentiated from the loose associations that often characterize the speech of a schizophrenic patient. The manic patient's racing thoughts may at first appear to be disjointed; however, on closer listening, one can usually discern a chain of superficial associations that give a certain structure to it. The following is an example of flight of ideas in a dialogue with a manic patient:

How did I sleep? Well, thank you! I had coffee and toast for breakfast with strawberry jam which was too sweet. Did you read the latest the Americans found out on saccharine? Rats do not get cancer from it. Only the Canadians said so, and their dollar is now down to 80¢ of ours . . . . You look like a Cancer to me, I am a Libra . . . .

In the schizophrenic's tangential or dissociated speech, the links between components, if they can be discerned at all, are more symbolic—or grossly concrete—and not as transparent and superficial as in the manic's flight of ideas. Occasionally, manic patients' pressure of speech and flight of ideas are so pronounced that their sentence structure is disrupted, and they talk in an almost incomprehensible telegram style.

Perhaps the most characteristic features of the manic state are euphoria and disinhibition. These lead to the well-known grandiosity and impaired judgment that draws so many manic patients into ill-advised business gambles, financial overcommitments, and, above all, big personal spending sprees—often including enormous bills for long-distance calls.

A 42-year-old man who was running a successful small clothing store became hypomanic and, with typical hypomanic persuasiveness, convinced a bank manager to extend a substantial loan with which to open five new downtown offices, each with a telephone, secretary, and sizeable inventory—without thinking through a management or marketing plan. The whole enterprise collapsed when he became fully manic, and after recovery from his illness, he was faced with a $300,000 business debt.

Manic individuals are often plausible, witty, and convincing talkers—not only with bank managers but also with unwary physicians. The distraught family may insist that something is badly wrong, but the manic patient sometimes can convince the physician that the family is simply "behind the times" and does not appreciate the patient's real talents, ability, and financial acumen.

In many ways the manic person acts as if intoxicated, exhibiting impulsiveness, reacting with rage when provoked, and sometimes taking extraordinary risks. Manic individuals almost always overestimate their capacities—intellectual, physical, social, or financial—and may be virtually immune to both pain and fatigue, sometimes disguising important somatic symptoms. As a rule, manic patients lack insight and do not realize that they are not well. They are likely to become irritated at anyone suggesting that they seek help and may threaten with litigation, making it difficult to treat them, short of the later stages of this condition in which they might have to be involuntarily committed to a hospital and after which much serious destruction may have been done to their lives and those of their families.

An acutely manic psychiatrist who had threatened this author angrily with a $500,000 libel-malpractice suit while being treated in hospital, described, after his recovery, the embarrassment he had felt, even as he was making these threats, and was, at the same time, remembering similar "sick" threats he had received from manic patients that he had treated. Nevertheless, he could not stop himself from talking in an equally ridiculous way, and that had made him even angrier at the time.

Hypersexuality, seductiveness, promiscuity, and indiscretion are frequent aspects of the manic patient's disinhibition.

A 24-year old housewife who ordinarily led a conventional life with strict moral standards started to frequent singles' bars and engage in various sexual relationships before her manic condition was diagnosed.

A hypomanic physician acquired a mistress, brought her to his home a week later, and was surprised when his wife resented being introduced to this woman.

As with depressed patients, about 15 to 20 percent of manic patients develop psychotic states with the presence of hallucinations and delusions that are mood-congruent. That is, in the case of a manic patient, the content of the hallucinations would indicate expansiveness, grandiosity, and euphoria (Table 18.5–8).

A well-developed, mood-congruent paranoid system may appear during a manic episode:

A manic man was convinced that an organized ring of beautiful women, disguised as waitresses, was covering all restaurants that he frequented. This arrangement was being paid for by an unknown

TABLE 18.5–8
Diagnostic Features of Manic Episode with Psychosis*

Essential Features	*Associated Features*	*Other Features†*
A. Meets criteria for manic episode B. Gross impairment in reality testing as expressed either in hallucinations, delusions, or grossly inappropriate behavior	Hallucinations or delusions may be mood-congruent or mood-incongruent	Differential diagnosis between manic episode, schizoaffective disorder, schizophrenia, and particularly organic or toxic (substance abuse) mental disorder must be considered

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.
† Not cited as a clinical feature in DSM-III, but may be present in these disorders.

TABLE 18.5–9
Diagnostic Features of Bipolar Disorder, Depressed*

Essential Features	*Associated Features*	*Other Features†*
A. Has had at least one manic episode B. Currently in a major depressive episode (or in a depression not meeting the full criteria for a major depressive episode provided there is a history of a previous one)	From 0.4 to 1.2 percent of the adult population are estimated to have had bipolar disorder that, in contrast to unipolar disorder, is probably equally common in women and men There is often a family history of major affective disorder	Onset tends to be earlier than that of unipolar major depressive episode First episode often manic

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.
† Not cited as a clinical feature in DSM-III, but may be present in these disorders.

man who had recognized the patient's superior abilities and charm and wanted him as a future business partner.

DIFFERENTIAL DIAGNOSIS

DEPRESSIVE STATES As yet there are no unequivocal signs, symptoms, or objective criteria for the diagnosis of affective disorders, either depressive or manic states. Clinical observation, the patient's history, and the physician's empathy are the ways by which the clinician has to make a diagnosis. In the past, the differential diagnosis of psychiatric disorders depended thus entirely on the diagnostician's clinical competence and experience. Today, this diagnostic process is greatly facilitated by well-structured interview schedules and carefully defined symptom lists that are available in several languages. ICD-9 is accepted as the official standard for most countries, but DSM-III is the official diagnostic guide for the United States. It is derived from the well-known RDC and is characterized by rigorous adherence to operational definitions of all diagnosable psychiatric disorders. The reader is referred to Tables 18.5–1, –2, –5, –6, –7, –8, –9, –10, –14, and –15, which were adapted from DSM-III, for a comprehensive listing of psychiatric symptoms and syndromes and is referred to the standardized principles and procedural rules of DSM-III for the differential diagnostic process. Some additional comments that follow may help to supplement this process in individual cases.

History of illness A good history of previous illness, as well as family history, are indispensable tools of diagnosis of affective disorders, the essential characteristic of which is their episodicity, frequently with a genetic background. The patient's premorbid functioning in the areas of social and work adjustment should be ascertained; in affective disorders this is usually of normal or superior level. A positive history of psychiatric illness, particularly of depressive or manic episodes or of suicide in the family, is significant. A personal history of depressive or manic episodes in the past may be pathognomonic. Although it may not be difficult to elicit a history of past depressions, it is well recognized that it can be difficult to establish an accurate history of manic episodes.

When patients are asked whether they ever felt better than usual, more elated, active, "high," they will often answer that they did feel that way when they were on vacation or when they graduated from college. The examiner must make sure that the patients refer to a condition that was peculiar because it persisted for more than 1 week, was noted by other persons in the environment to be strange, and involved unusual and inappropriate behavior, e.g. buying sprees or greatly increased sociability.

Even depressive episodes may not be recalled with precision by the patient if the examiner wants to know the exact dates of the beginning and, particularly, the end of each past episode. Often only some improvement and then a prolonged period of anxiety, or vague other symptoms, can be remembered.

Unipolar–bipolar disorder Most clinicians accept one manic episode as a criterion of bipolar disorder (Table 18.5–9). Unipolar manic disorders do exist but are rare. It has been pointed out that the symptoms of unipolar and bipolar manic syndromes are identical and that this fact does not support a distinction between unipolar and bipolar manic patients. The same argument can be made regarding unipolar and bipolar depressions; but in that case the distinction is not based on different symptomatology but on a different course, age of onset, and family history. DSM-III has assumed, nevertheless, the convention to classify unipolar manic illness under bipolar affective disorder.

A distinction between bipolar I and bipolar II disorder has been proposed, the first referring to spontaneously occurring, clinical manic episodes and the second to mild, subclinical episodes or to those manic states that occur only as a reaction to antidepressant, mostly tricyclic pharmacotherapy. The clinical value of this distinction is questionable.

Identifying pathological depression Before a physician can make a diagnosis or formulate a treatment plan, the presence of a clinically depressed state must be recognized in the patient. Then the physician will have to differentiate between a grief reaction and a truly pathological condition requiring clinical treatment (Fig. 18.5–8).

There is frequently an elusive dividing line between the two, to which DSM-III refers under "depression with melan-

cholia" as having a "distinct quality of depressed mood"; that is, the depressed mood is perceived as distinctly "different from the kind of feeling experienced following the death of a loved one" (Table 18.5–10).

Although this quality tends to be distinct indeed to the patient, it may be far less distinct to the observer—psychiatrist, family doctor, relative, or friend. Clinical depression may appear deceivingly similar in its expression to ordinary grief, with both frequently described by such adjectives as numbness, aloneness, unfeelingness, and even the complete inability to experience interest in anything.

Pathological affect or normal mood swing? A key problem with affective disorders—manic or depressive—is that their very existence may not be recognized. In a masked depression, for instance, the depressive affect may be so well disguised by other symptoms, such as somatic ones, that the examining physician may miss it entirely. Even if a depressive or manic state is recognized, it may not be identified as a clinical condition but may be mistaken for an ordinary mood swing. Conversely, normal emotional reactions, e.g. grief or normal elation, may be mistakenly diagnosed as pathological conditions.

Failure to take a good clinical history, or to consider the context of the patient's current life situation, might lead to these errors. How, then, can the diagnostician recognize a clinical condition as opposed to a pronounced, but not pathological, mood swing?

TABLE 18.5–10
Diagnostic Features of Major Depressive Episode with Melancholia*

Essential Features	*Other Features*†
A. Loss of pleasure in almost all activities	Great danger of suicide completion
B. Loss of all responsiveness to usually pleasurable stimuli	
C. Three of the following:	
1. Distinct quality of depressed mood, i.e. different from the sadness experienced following the death of a loved one	
2. Feels worse in the morning	
3. Early morning awakening (at least 2 hours before usual time)	
4. Marked psychomotor retardation or agitation	
5. Anorexia or weight loss	
6. Inappropriate or excessive guilt	

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.

† Not cited as a clinical feature in DSM-III, but may be present in these disorders.

A pathological affective state can be diagnosed either by its excessive duration and intensity or by the absence of a traumatic stress situation in the recent history of the patient.

Probably only a minority of depressed patients come for treatment and are treated appropriately when they do come.

FIGURE 18.5–8. *Two oil paintings by a 40-year-old woman amateur painter.* A *was produced during a major depressive episode;* B *three months later, after recovery. (Courtesy of M Amin, MD, Montreal.)*

TABLE 18.5–11
Depressive Symptoms According to Clinical and Logical Dimensions

Somatic Behavioral	*Psychological*	*Organismic*
Not sufficient; not necessary:	Sufficient; not necessary:	Necessary:
Disorders of: Appetite, Digestion, Weight, Sleep, Libido	1. Depressed mood 2. Hopelessness 3. Ruminations (over loss or guilt)	Invariant core syndrome of negative behavioral symptoms: 1. Reduction of interest (apathy) 2. Reduction of capacity to enjoy (anhedonia) 3. Reduction of energy (asthenia)
Presence of: Fatigue, Pain		
Suicide		

Many are reluctant to seek help, particularly when not all symptoms are specific and complaints include exhaustion, "burnout," "nerves," acute or chronic anxiety, or a variety of somatic symptoms.

In the physician's office, questions arise too. Is a person who complains of lack of sleep, poor appetite, inability to concentrate, disinclination to work, and social withdrawal suffering from depression or from chronic anxiety?

A young man complains of feeling "lousy and fed up" every morning, shows increased irritability, avoidance of contact with family, loss of sexual interest in his live-in partner. Is he depressed, or is he angry?

Necessary and sufficient symptoms of depression Because many of the symptoms that are most frequently found in depressions are nonspecific and may also occur in primary anxiety and other dysphoric states or in various psychosomatic disorders, it may be useful to consider a logical device to assist with the differentiation. It is possible to view depressive symptoms under the three categories of (1) functional-behavioral, (2) psychological, or (3) organismic symptoms. The first category of symptoms is regarded as not sufficient and not necessary, the second is sufficient but not necessary, and the third is necessary but not sufficient (Table 18.5–11).

In the first category, there are the typical accessory symptoms of depression—e.g. sleep and appetite disturbances, loss of sexual drive, feelings of guilt or inadequacy, persistent fatigue, as well as suicidal ideation or behavior—all of which are common in depression but may also occur in conditions that are not primarily depressive.

In the second category, there are depressed mood, hopelessness, or unending ruminations over loss or guilt. The presence of these symptoms by themselves is sufficient to make a diagnosis of depression because these are specific pathognomonic symptoms, but they are not necessary, and their absence does not rule out a diagnosis of depression.

Finally, in the third category, there is a triad of necessary symptoms that remains probably invariant throughout all cultures and is crucial for the diagnosis of any depression. In many surveys these symptoms regularly have been found among the five or six most frequent symptoms, right after depressed mood (sadness) and anxiety. If at least two of the three symptoms of apathy (lack of interest), anhedonia (joylessness), and asthenia (lack of energy) have been present for more than a month—and provided other pathology, e.g. physical disease, has been eliminated—a diagnosis of depression should be seriously considered, even if other specific or typical depressive symptoms are not apparent.

Anxiety versus depression A patient whose primary symptom is anxiety seldom complains about loss of interest in everyday activities, work, hobbies, and so on. In fact, there may be overindulging in recreational or other leisure activities, or overcompensating by adding social contacts to the usual schedule. Although there may be complaints of fatigue and lack of energy, productivity may not be reduced but may actually be increased, except in those particular areas that are directly related to the patient's anxiety. By contrast, the severely depressed individual usually suffers from complete, global fatigue. Furthermore, the anxious individual is capable of enjoying pleasurable activities more frequently than the depressed.

Psychotic depressions Here, the touchstones are the presence of hallucinations, delusions, thought disorder, or grossly inappropriate behavior, as well as the mood-congruency of hallucinations or delusions (Table 18.5–1). If a person who appears depressed is having auditory hallucinations that are telling him that he is Jesus Christ and that his mission is to save the world from World War III, their content would not be mood-congruent—that is, consistent with a diagnosis of primary affective disorder of the depressed type—because the patient's self-perception is more grandiose than self-deprecatory.

Similarly, ominous delusions of cosmic annihilation, expressed by a manic patient, would be judged to be mood-incongruent. In this case a diagnosis of primary affective disorder would have to be seriously questioned, and other diagnoses, such as schizophrenia, schizoaffective disorder, atypical, organic, or drug-induced psychoses, would have to be considered.

Depression in the aged Physicians in ancient Greece and Rome tied black bile, melancholia, and old age together into an inescapable cluster. Today, although clinicians have long since separated old age from depression, the two still occur together with disproportionate frequency, and depression in the elderly is often overlooked behind the stereotyped diagnosis of senility. In many such cases, senility is not present but clinical depression is.

Pseudodementia is a condition commonly associated with depression in the elderly, in whom cognitive symptoms of an organic brain syndrome, e.g. impaired memory, confusion, disorientation, may appear. When the depression is relieved, the symptoms of the secondary pseudodementia also are reversed. Unfortunately, such symptoms are often misdiagnosed as primary, progressive, and irreversible dementia of the Alzheimer type and thus assumed to be untreatable.

Psychological tests may be helpful in the diagnostic assessment of a patient, in particular those procedures that are best suited to the detection of early signs of organic cognitive and perceptual impairment, e.g. the Mini-Mental State or the Bender-Gestalt Test. Laboratory procedures, such as the electroencephalogram (EEG), the computed tomography (CT) scan, or measures of cerebral blood flow, are other aids to the diagnosis of primary brain disease and progressive dementia, but they frequently result in false-positive as well as false-negative diagnoses. They should not be used as decisive criteria.

A clinician might commit a serious diagnostic error by assuming that a slowing of the α-rhythm in the EEG or some cortical atrophy on the CT scan of a patient clearly establishes the diagnosis of primary progressive dementia. Whenever

there is uncertainty about a diagnosis of depression in the elderly, good clinical practice dictates an adequate trial of antidepressant therapy as a diagnostic procedure.

Depression in children Until recently, pediatricians did not diagnose depression in children, citing the prevailing psychiatric theory that depression could not occur until an individual reached a certain level of intellectual development or ego maturation.

Today it is known that not only do depressions occur in children but also that they are not uncommon. As would be expected, the incidence of childhood depression in the general population is relatively low, but among children being treated for behavior disorders in psychiatric facilities, the prevalence of depression has been shown to be between 10 and 25 percent.

At midcentury the picture of anaclitic depression (in DSM-III, reactive attachment disorder of infancy) was first described in orphaned infants who, deprived of mothering, developed a syndrome that had already been well known to animal breeders and naturalists. The babies stopped growing, did not thrive, or in some cases regressed physically, emotionally, socially, and cognitively.

Depressions in children often are not diagnosed and may be treated as behavior disorders, adolescent turmoil, or even early schizophrenia because social withdrawal and learning difficulties may be the principal symptoms of depression in children and acting out a significant depressive manifestation in adolescents. Failure to diagnose and treat depressions in the young and the aged may be responsible for the alarmingly high, and still rising, suicide rates in these two age groups.

In recent years, clinicians have identified a significant group of children who, even at prepubertal age, present with the typical depressive picture of adults. These children usually respond to the established antidepressant pharmacotherapies although they often may not show the physiological changes or biological markers (metabolic, endocrine, sleep) that are characteristic of adult depressive states.

Affective disorder secondary to somatic disease Many depressive, and a small number of manic, states are secondary conditions associated with physical diseases or the use of drugs, and because the distinction between primary and secondary affective disorders cannot be made reliably on the basis of symptoms alone, it is essential to perform a thorough physical examination on every patient and obtain a detailed drug history in each case. It has been found that about 20 percent of all patients hospitalized for some medical condition have depressive symptoms. Tables 18.5–12 and 18.5–13 give some of the diseases and drugs most commonly associated with depressive or manic disorders. The interaction of these physical conditions and their treatment with the effects and treatment of the affective disorder must be carefully considered before treatment plans are developed.

TABLE 18.5–12
Somatic Disorders That May Be Causally Related to Depressive Syndromes

Cardiovascular	Over 60 percent of hospitalized cardiac patients are depressed. Eighteen months after a myocardial infarction, one-third of patients develop a depression.
Gastrointestinal	It may be difficult to recognize what comes first—gastrointestinal or depressive symptoms.
Neurological	Symptoms of Huntington's disease, brain tumors, and primary dementias are frequently preceded by or associated with depression. As many as 25 percent of patients with multiple sclerosis may be depressed.
Diseases of the pancreas	
Hypothyroidism	
Hyperthyroidism	In the form of apathetic thyrotoxicosis.
Hyperparathyroidism	
Addison's disease	
Cushing's disease	
Rheumatoid arthritis	Between 40 to 50 percent of patients show depressive features.
Infectious diseases	Particularly virus diseases, e.g. mononucleosis.
Various neoplasms	Depression is sometimes the first manifestation. More than 40 percent of cancer patients, especially those receiving chemotherapy, show depressive symptoms.
Malnutrition	Elderly people, because of poor eating habits and impaired absorption, are highly susceptible to protein and vitamin (B) deficiencies and resulting depression.

TABLE 18.5–13
Commonly Used Drugs That May Be Causally Related to Depressive Syndromes

Psychotropic Drugs	Antipsychotic agents (phenothiazines; butyrophenones); barbiturates; meprobamate; benzodiazepines; a variety of "street" drugs
Corticosteroids	Also may induce manic states
L-Dopa	Also may induce manic states
Digitalis	More frequently induces toxic psychosis
Antihypertensive drugs	Most frequently reserpine (in about 10 percent); alpha-methyldopa; propranolol; hydralazine; guanethidine; clonidine
Cocaine	May induce manic states

Biological markers Biological measures, the Holy Grail of psychiatric diagnosis for which so many investigators are now searching, might eventually yield a small cluster of clearly defined biological markers by which affective disorders could be truly objectively determined; that is, by pointer readings. Among the more promising markers that have been proposed—some being used experimentally, others already for actual clinical diagnosis—are the dexamethasone suppression test (DST); thyrotropin-releasing hormone (TRH) stimulating test and growth hormone tests; levels of neurotransmitter metabolites, particularly the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) in CSF, as well as catecholamine metabolites, e.g. 3-methoxy-4-hydroxyphenylglycol (MHPG), and cortisol levels in the plasma and urine; choline uptake by erythrocytes; and affinity of imipramine and serotonin to platelets. Another fairly specific biological marker for depression is an alteration of the EEG sleep profile, more particularly a reduced latency of rapid eye movement (REM) sleep. These sleep factors, which are almost universally present in adult major depressive episodes, have recently been found to be absent in the depressions of children of prepubertal age, and in general, none of the other biological markers are as sensitive and specific as would be desirable for practical clinical use.

The DST, for which by far the most comprehensive data are available, has been the most promising biological marker, with a reported sensitivity close to 50 percent for endogenous depressions and a specificity of over 90 percent, until it was found that advanced age, Alzheimer's disease, alcoholism, recent loss of weight, mixed manic-depressive episodes, and

other conditions are also associated with a positive DST. Unless the screening for this test is further qualified, there would be too many false-positive results for endogenous, or biologically determined, depression.

Because the DST is a state-dependent rather than a trait-dependent marker, it could still be a monitoring device of a depressed patient's condition after all acute symptoms have subsided, to indicate at what time a patient's pharmacotherapy might be reduced or discontinued or when a symptom-free patient may be approaching a relapse. This role of DST must also be qualified because recent studies have shown that the test is not a reliable indicator of a patient's condition if the patient has been receiving electroconvulsive therapy (ECT) or lithium.

It is probable that the chief value of any biological marker for affective disorders ultimately will lie in its role as a criterion for biological classification. Today, the diagnosis of a depressive, or unipolar or bipolar manic, condition presents no particular problems to the average, well-trained clinician who relies only on his or her own examination. In fact, the diagnosis of a bipolar affective disorder is one of the most reliable psychiatric diagnoses that can be made today, but the choice of a specific treatment is still mainly based on trial and error. Further refinement of classification, according to special symptom patterns, genetic data, and biological markers, will eventually give the key to more systematic, objective, and reliable indications for treatment.

THE MANIC SYNDROME The manic syndrome does not present quite as many differential diagnostic difficulties because there is little likelihood that a manic syndrome is the result of purely psychogenic factors (Table 18.5–7). A differential diagnosis must primarily consider drug-induced states—usually of short duration—and organic brain disease, e.g. tumors in the frontal lobe or midbrain area. Until the introduction of penicillin in the 1940s, the differential diagnosis between a primary manic state and general paresis of the insane (syphilitic meningoencephalitis) was often difficult during the early stages of this brain disease, as long as it was entirely based on symptomatology; and a diagnosis frequently could not be made with certainty until serological findings became available.

Of course, the history of recent drug abuse or the presence of characteristic organic brain symptoms, such as memory loss, confusion, and disorientation, might quickly settle the issue in favor of a toxic or an organic brain disease.

The confused manic It is not unusual for a manic patient who has just been admitted to a hospital to be in a state of exhaustion, and after several sleepless nights and days without adequate food or liquids, to be suffering from a toxic-exhaustive delirium, superimposed on a manic condition. The patient may now present symptoms of confusion, disorientation, and incoherent speech. These symptoms subside in most cases, and the underlying manic condition becomes evident as soon as the toxic-exhaustion syndrome has been successfully treated. If the patient requires heavy doses of medication, the confusion may not clear completely for considerable time.

Manic versus schizophrenic excitement The possibility of an excited, catatonic syndrome of schizophrenia will sometimes have to be considered, particularly during the first week or two after the acute onset of a manic syndrome. If this is the first manic episode in a patient over 50 years of age, schizophrenia can usually be ruled out on this basis alone. Under clinical observation, the rapid emergence of more typically schizophrenic symptoms, such as sustained thought disorder, mood-incongruent delusions, and hallucinations, as well as the premorbid personality, should, within a week or two, leave no doubt about the final diagnosis.

One of the key distinctions between excited states of the affective and schizophrenic type is the patients' contact with reality, as assessed by responses to external stimuli. In cases of manic patients suffering from an affective disorder, their contact with the environment would be exaggerated, their distractibility compelling them to respond to a multitude of environmental stimuli; whereas, schizophrenic patients are primarily preoccupied with, and driven by, internal stimuli and usually pay only limited attention to their physical surroundings.

Casual diagnostic observations Two diagnostic clues to the diagnosis in a manic patient may be mentioned here: (1) This writer has found that virtually all patients who, after having been presented before a group of staff members or medical students, thank the examiner when they are leaving may be diagnosed as manic—probably, because only a superoptimistic, overly gregarious manic would truly enjoy such a meeting. (2) Any patients who, as many manic patients do, state that they feel "better than ever" in their lives are almost certainly suffering from a manic disorder.

Affective symptoms and schizophrenia If depressive or manic symptoms are present in a schizophrenic patient, it is important to determine whether the affective symptoms represent an episodic syndrome that is superimposed on the schizophrenia, whether they are side effects of neuroleptic pharmacotherapy, or whether they are part of the basic, symptomatic repertoire of the underlying schizophrenia that may be of the acute or the residual type. Either case might call for a different therapeutic strategy.

Other specific affective disorders DSM-III distinguishes two other diagnostic categories of affective illness, dysthymic and cyclothymic disorders. The symptoms, extracted from this reference and detailed on Tables 18.5–14 and 18.5–15, closely resemble those of the unipolar (depressive) and bipolar (manic or depressive) states, except that they are always chronic and usually are less severe and less disabling. They are never associated with psychotic symptoms.

Dysthymic disorders Depressive neuroses resemble unipolar depressions, but symptoms are less acute and less disabling. They may be persistent from an early age (even childhood) or intermittent, but intervals of normal moods never last more than a few weeks or months. There are no episodes of elevated mood. Onset is not clear or acute. The course is always chronic, and as with major depressions, the disorder is seen more frequently in females, although in children it seems to be equally common in both sexes. People suffering from dysthmic disorders are likely to view their handicap more as a character trait than as an illness (Table 18.5–14).

The diagnostic picture becomes blurred when an acute major depression or a full-blown manic episode is superimposed on a preexisting dysthymic or cyclothymic condition. A distinction must be made, when a major depressive episode does not fully remit, between a chronic depression and an acute depressive episode occurring on top of a dysthymic disorder. In such a case, DSM-III calls for a 2-fold diagnosis on Axis I: a major depression and dysthymic disorder.

If a clinician knows that a patient has been dysthymic or cyclothymic before the onset of an acute episode, full recovery

TABLE 18.5–14
Diagnostic Features of Dysthymic Disorder*

Essential Features	*Associated Features*
A. During the past 2 years depressive symptoms that do not meet the full criteria for a major depressive episode	Other name: depressive neurosis
B. The depressive symptoms may have been continuous or interrupted by relatively short periods of normal mood, never lasting more than a few months at a time	Frequently associated with personality disorder
C. There is either typically depressed mood or loss of interest or pleasure in most usual activities	Onset usually early in adolescence or adult life
D. During depressive periods at least three of the following are present:	In children, school performance may be affected
1. Insomnia or hypersomnia	Chronic course
2. Low energy	Chronic physical disorder or psychosocial stressor is often predisposing factor
3. Feelings of inadequacy, low self-esteem	Differential diagnosis between major depressive episode, personality disorder (borderline, histrionic, dependent), and other chronic mental disorders sometimes difficult
4. Decreased effectiveness at work or studying	Dysthymic disorder may be superimposed on other disorders and should then be recorded as a separate diagnosis
5. Reduced concentration	
6. Social withdrawal	
7. Loss of interest and enjoyment	
8. Increased irritability	
9. Inability to be pleased by praise	
10. Less active or talkative; slowed down or restless	
11. Brooding, pessimistic, or sorry for self	
12. Tearfulness, crying	
13. Thoughts of death or suicide	
E. Absence of psychotic symptoms	
F. If superimposed on other mental disorder, e.g. obsessive-compulsive disorder or alcohol dependence, the depressed mood is clearly different from the person's usual mood	

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington, DC, 1980.

should not be expected, and futile, overlong therapeutic approaches should be avoided.

Cyclothymic disorder Relatively common, this disorder usually starts in early adulthood and occurs more often in women than men, in contrast to full-blown bipolar affective disorder where the distribution between the sexes is equal. It is more common in families with members suffering from major affective disorders.

The affective symptoms tend to be muted, e.g. loss of interest or pleasure, instead of feelings of hopelessness and depression; irritable or expansive mood, instead of manic euphoria. The chronic nature of cyclothymic disorder may cause considerable social and occupational impairment; however, because of the insidious onset and long duration, affected people often have learned how to cope, at least partially, with their symptoms. If they seek help at all, they are more likely to go to a family physician than to a psychiatrist, because both patients and family members may consider symptoms more as character traits than pathological symptoms (Table 18.5–15).

Because of their chronically unbalanced mood, patients often seek an antidote to their lack of pleasure in alcohol or drugs and may indulge in excessive drinking during their more euphoric states. They may even applaud the increases of energy and the sharpened, sometimes creative, thinking that come with the hypomanic periods.

This author joins many other psychiatrists in viewing the cyclothymic disorder not as an independent entity, but simply as a mild form of bipolar affective disorder. The dysthymic disorder is seen either as a mild, chronic endogenous depression or as a psychogenic depressive neurosis. The latter view is held by ICD-9, which defines neurotic depression as usually following a distressing experience. Others argue that at least some of these specific affective disorders should be classed with personality or character disorders. The differential diagnosis between borderline states, dependent personality disorder, and dysthymic disorder may be very difficult in some cases.

Atypical depression If a depressive syndrome occurs in a residual schizophrenic, or in a patient who fulfills the criteria of dysthymic disorder but has had normal periods lasting more than a few months, or if the episode is brief and fails to meet the criteria for a major affective disorder and is not reactive to psychosocial stress, then a diagnosis of atypical depression is indicated according to DSM-III. Cyclothymic disorder should be considered if manic syndromes have been observed also.

Schizoaffective disorder If clearly affective symptoms are mixed with symptoms more characteristic of schizophrenia—for instance, prominent depression with thought disorder and mood-incongruent auditory hallucinations—a diagnosis of schizoaffective disorder must be considered. This condition has been traditionally treated as a subgroup of schizophrenia, although some authors claim it to be a variant of the affective disorders. DSM-III has established a separate category of schizoaffective disorder and deals with it as an autonomous disease.

Switching diagnoses Diagnostic changes are sometimes indicated when, over a period of years, a typical affective disorder may change into a picture of typical schizophrenia. More rarely the reverse may also occur, particularly if the onset of schizophrenia was early in life and the symptoms confounded by those of adolescent turmoil. A switch of diagnosis over time from affective to schizoaffective disorder is estimated to occur in 7 to 10 percent of cases.

Variable prevalence of diagnoses The diagnosis of affective disorders, similar to schizophrenia, has shown different prevalence in different countries and undergone several changes over the years. In the 1940s and 1950s manic-depressive disorder was generally considered to be a comparatively rare disease; nevertheless, in 1961 it was 9 times as often diagnosed in Great Britain as in the United States. Then, a major study of diagnostic practices in the United Kingdom and the United States revealed that American psychiatrists

TABLE 18.5-15
Diagnostic Features of Cyclothymic Disorder*

Essential Features		*Associated Features*	*Other Features†*
A. During the last 2 years many periods with symptoms of depressive and manic syndromes not sufficiently severe or lasting to meet criteria for major depressive or manic episodes		Frequently alcohol and other substance abuse	The changing and sustained moods and behaviors of patients with cyclothymic disorder are often responsible for serious marital problems
B. There may be periods of normal mood, lasting for months, between the depressive and hypomanic episodes that usually are not regularly spaced		Tends to have chronic course	
		More common among outpatients than previously assumed	
C. During *depressive periods* there is depressed mood, loss of interest and pleasure, and at least three of the following:	During *hypomanic periods* there is an elevated, expansive, or irritable mood and at least three of the following:	Often family history of bipolar disorder and major depression	
1. Insomnia or hypersomnia	1. Reduced need for sleep		
2. Low energy	2. Increased energy		
3. Feelings of inadequacy	3. Increased self-esteem		
4. Depressed effectiveness at work or studying	4. Increased productivity and long, unusual working hours		
5. Decreased concentration	5. Sharpened, creative thinking		
6. Social withdrawal	6. Uninhibited gregariousness		
7. Loss of interest in sex	7. Uninhibited and excessive sexuality		
8. Guilt over past activities	8. Irresponsibility and poor judgment, e.g. buying sprees, foolish investments, reckless driving		
9. Feeling slowed down	9. Restlessness		
10. Less talkative than usual	10. More talkative than usual		
11. Brooding and pessimism	11. Excessive optimism		
12. Tearfulness	12. Inappropriate laughing and joking		
D. Absence of psychotic features			
E. Not due to any other mental disorder, e.g. partial remission of bipolar disorder			

* Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3. American Psychiatric Association, Washington , DC, 1980.
† Not cited as a clinical feature in DSM-III, but may be present in these disorders.

had a strong predilection for the diagnosis of schizophrenia and, consequently, diagnosed affective disorders too rarely. In the 1970s the diagnosis of affective disorders increased significantly, not only because, at least in the United States, the diagnosis of schizophrenia was now made with more discrimination, but also because lithium had been introduced as an effective therapeutic agent for affective disorders. Although, logically, treatment should be regulated by diagnosis, history has shown repeatedly that the availability of a new specific and successful treatment leads to more frequent diagnoses of the condition for which the treatment is indicated.

RATING SCALES AND OTHER DIAGNOSTIC DEVICES

Diagnostic instruments in psychiatry include behavior rating scales, symptom check lists, structured interviews, personality inventories, projective tests, and psychometric procedures. The selection from among them depends on the purpose for which the instrument is chosen.

If the intent is to screen a general population for a specific disorder, it is important that the instrument be easily administered. Its other characteristics are determined by the primary need to avoid as many false-negative results as possible by casting a wide net or to avoid false-positive results by using a fine filter. In the first case, a device of high sensitivity is needed; in the second, a measure of high specificity.

For the clinician it is more important to avoid false-negatives (high sensitivity), for the researcher to avoid false-positives (high specificity). At least, this is valid for the neuroscientist who needs patient groups of the highest homogeneity for biologically focused research; whereas, an epidemiologist, inquiring into the prevalence of a disorder, may be more interested in an instrument of higher sensitivity.

The clinician psychiatrist cannot yet—and perhaps never will—depend entirely on test results for final differential diagnosis, but may find structured interviews and personality inventories useful because their comprehensiveness will be protection against overlooking certain symptoms and, at the same time, will increase the objectivity of the examination and its comparability to the findings of other examiners.

Ever since the introduction of effective antidepressant and antimanic drug treatment, the quantification of the severity of affective disorders has become a significant development. Hence, most rating scales for depressive and manic episodes are administered periodically and monitor and score the course of a clinical episode and the effects of pharmacotherapy on it.

Self-administered versus examiner-administered scales Some rating scales and inventories are self-administered by the subject; others must be completed by physicians or nurses. Self-administration has the advantages of saving time for the medical personnel and of giving access to subjective experiences that may not be adequately expressed and may be missed by other observers. Disadvantages of self-administration are complete subjectivity and, possibly, intentional or unintentional misinformation, e.g. if the subject is unwilling to reveal the responses made or has misunderstood questions.

Symptom versus syndrome rating Most rating scales are best suited to take an inventory of all symptoms that are frequently associated with a depressive syndrome. A few scales are oriented more toward the detection of a particular pattern of symptoms, i.e. a depressive syndrome. This is an important consideration for epidemiological surveys with rating scales that sometimes show a prevalence of 20 percent of depressive symptoms in a population that has only a prevalence of 3 to

4 percent of depressive syndromes, i.e. depressive conditions of clinical significance.

No rating scale, whether administered by the patient or the interviewer, is usable in patients suffering from very severe depression, because such patients are not capable of giving any detailed information nor are they accessible to any questioning.

The ideal scale A good rating scale must be constructed on the basis of both clinical experience and statistical analysis. It must be validated—that is, proved that the scale really measures what it claims to measure—and its reliability, both between different raters (interrater) and at different points in time (test-retest), must be demonstrated. It must also be comprehensive and balanced, e.g. not be greatly biased toward the assessment of psychomotor or psychic or verbal features. Also it should be fairly brief and simple. The listing of all these desiderata explains why no ideal rating scale exists today. In the search for ever-better scales, so many of these devices used in the assessment of affective disorders have been developed that some observers have called for a moratorium on new rating scales of this type until the relative values and applications of the existing ones have been appraised.

Most of the numerous rating scales for the assessment of affective disorders involve depressive states. Because manic conditions occur far less frequently, there has been lower interest in developing scales to rate these states.

Functions of scaling devices In general, one can divide the types of scaling devices for the rating of affective disorders according to three functions:

1. Quantitative measurement of severity of the disorder;
2. Qualitative, i.e. diagnostic identification of special patterns; and
3. Classification of personality characteristics for the prediction of risk and treatment response.

Projective tests, such as the Rorschach or Thematic Apperception Test, that mainly probe imagery and fantasy, as these functions reflect ego structure and defense mechanisms, are of little use in the affective disorders. Psychometric procedures also are rarely called on in these conditions, and if they are used, it is as adjunctive measures of the severity of the disorder, for instance as it impairs concentration or problem solving.

Only a few of the many available scales can be mentioned here, and the author's choice will be determined by the current distribution of their use, as well as by the specific functions they can serve.

Hamilton Depression Rating Scale For the measurement of the severity of depressive states, the Hamilton Depression Rating Scale (HDRS) is probably best known. It is designed to be administered by an interviewer. Several modifications of its original version have been developed, but in its most widely used form it comprises 17 items. Of these, 9 items are scored on a five-point scale and 8 items on a three-point ordinal scale. HDRS was constructed for use with patients already diagnosed as depressed, but has also been used for general medical patients. Its main function is the quantitative assessment of the severity of depressive states.

Beck Depression Inventory A second popular scale for the quantitative assessment of depressive conditions is the Beck Depression Inventory (BDI). It was one of the first self-administered scales. There are 21 items in the BDI, each statement to be rated by the patient on a scale from 0 to 3 to indicate the severity of the depression. To what extent the scale will be reliably completed depends greatly on the motivation of the patient, which, in turn, is related to the motivation of the examiner. Although the BDI and some of its subscales have been used for rapid diagnostic screening, this practice has pitfalls. For instance, in one group of intestinal-bypass surgical patients, the BDI seemed to measure asthenia more than depression.

Reliability of self-administered scales The Zung Scale is still another well-known, self-administered rating scale, but of late its credibility has been questioned, partly because of the number of scales to be completed by the subject. In general, the reliability of examiner-rated scales seems to be better than that of self-rated depression scales, according to several studies. This is certainly the case for scales rating manic states, as most manic patients rate themselves as normal or close to normal.

Orientation of scales The orientation of different scales may be important for clinicians because it provides access to specific areas of information. The HDRS, for instance, focuses on psychomotor symptoms, whereas a more recent scale, the Montgomery-Asberg Depression Rating Scale, centers primarily on the psychic symptoms of depression.

Diagnostic scales A few depression rating scales for diagnostic purposes exist. The best known are the Newcastle Scales (N-I and N-II), which were constructed to differentiate between endogenous and nonendogenous depressions, and the World Health Organization Standardized Assessment of Depressive Disorders (WHO/SADD), which was the diagnostic instrument in a major four-nation crosscultural study.

Spitzer and Endicott's structured interview Schedule for Affective Disorders and Schizophrenia is focused on two specific diagnostic areas.

The symptom checklists that form the substance for the operational definitions of DSM-III are, of course, most specific diagnostic devices.

Scales for manic states The first major scale for the quantitative assessment of manic states, Beigel's Manic-State Rating Scale (BMS), was designed by Beigel in 1971 more than 10 years after the publication of Hamilton's Depression Rating Scale. It is to be used by specially trained nurses, has 26 items to be defined for frequency and intensity, and has to be completed during an 8-hour period of observation. Several years later, Blackburn and a group of co-workers developed a frequently used revision of the BMS that they called Modified Manic Rating Scale. It has 28 items and can be rated by observers other than nurses.

Other rating scales for manic behavior have been designed by Petterson and co-workers, Bech and Rafaelsen, and Young and co-workers, but there are no self-rating, nor any diagnostic scales for manic behavior, unless one wants to consider the manic subscale of the Minnesota Multiple Personality Inventory (MMPI), which is not a symptom-rating scale.

Global assessment scales Instead of a total of different item scores, global assessment scores represent one over-all rating of the patient's condition. The most frequently used version of this mode of assessment is the visual analogue scale. It consists of a line, 10 cm in length, on which patients are required to indicate where they would locate their present

condition along a continuum running from normal to extremely depressed.

Personality inventories Finally, in addition to quantifying or diagnosing affective disorders by means of rating scales, it may well be that the information obtained by self-administered personality inventories, such as the MMPI or the Mark-Nyman Temperament Scale, may find some future application for the assessment of risk factors (vulnerability), for certain affective disorders, as well as for the prediction of treatment response.

It has long been claimed that certain varieties of body build, such as the pyknic or endomorphic type, are often associated with a specific personality structure, such as the cyclothymic type, as well as with a predisposition to bipolar affective disorder. More recent studies, including clinical trials, have shown that patients with certain personality characteristics tend to respond favorably to lithium treatment, even if they present with unipolar depressions. The concepts of *typus melancholicus* of recent German psychiatry and the "cohesive character" of the Japanese have been discussed under other headings of this section (see Classification and also Influence of History and Culture on Symptoms). These concepts also point toward a connection between personality structure and clinical factors in the affective disorders, a connection that requires further clarification in the future.

COURSE AND OUTCOME

Kraepelin distinguished manic-depressive psychosis from dementia precox or, as termed today, unipolar and bipolar affective disorders from schizophrenia not only by their symptomatology but also, and more importantly, by their periodic course and their outcome. Recurrent discrete episodes of mood disorder that do not lead to personality deterioration characterize affective disorders.

Their natural course is far more difficult to trace today than it was around the turn of the century when Kraepelin first formulated the concept of manic-depressive insanity, because most depressed and manic patients today receive antidepressant or antimanic therapy of some sort, and these interventions have shortened the length of individual episodes, as well as altered their pattern of periodicity.

Onset Bipolar disorders tend to start earlier than unipolar, usually in the third or fourth decade of life. Average age of onset is in the mid-twenties, but first episodes are not uncommon in late adolescence or early adulthood. In more than 50 percent of cases, the first episodes are depressions. Unipolar depressions also often start in the third and fourth decade, but reach their peak of incidence between the ages of 40 and 60 years. Among males, the incidence of depression increases with age, but in women in whom depressions tend to occur earlier than in men, their incidence no longer increases after the sixth decade of life. Reactive depressions tend to occur earlier than endogenous depressions.

Duration of episodes The duration of episodes, before the introduction of ECT treatment and pharmacotherapy, was given as from 2 months to several years, with an average of around 5 to 6 months. One-third of the patients then recovered within a year. The rest took longer, and probably, one out of four episodes became chronic and lasted more than 2 years. Manic episodes tended to be shorter than depressions.

How much time was spent in a hospital if a person was suffering from recurrent depressions or manic episodes? In the 1950s, when antidepressant drugs were first introduced, about half of those diagnosed manic-depressive spent more than 4 months in a hospital with each episode; 1 in 10 would be hospitalized over 4 years. The death rate from all causes for females was about twice the normal rate and for males three times the normal rate.

In the 1960s before the widespread use of preventive lithium therapy, a retrospective statistical study of the life history of manic-depressives concluded that these patients had episodes on average about every 2 to 3 years, each lasting about 4 months. If one assumes that a manic-depressive had the first breakdown at 25 years of age, then by the age of 60 the patient may have suffered 10 episodes and, with a conservative cumulative estimate, would have been ill a total of 3 to 4 years, with much of this time spent in a hospital.

Today, with modern treatment, the average duration of an individual bipolar episode is still 3 months, and 4 months in unipolar disorders, if the end point is taken as the disappearance of all symptoms. Patients generally improve substantially and may be functioning much sooner; that is, within 3 to 4 weeks from the start of adequate treatment. More than half of depressed patients recover in less than 2 to 3 months. General morbidity and mortality of affective disorders have also been significantly reduced with antidepressant and antimanic treatment, but about one in seven patients still becomes chronic.

Recurrences Kraepelin and a number of later observers believed that between 15 and 50 percent of patients have only one affective episode in their lives; others, using observation periods of up to 50 years, have come to the conclusion that virtually everyone who has been hospitalized once for depression will suffer more than one episode in a lifetime if the patient lives long enough. Thus, every affective disorder of significant severity should be considered to be a recurrent disease. Within a 5-year follow-up, about 25 percent of patients have no recurrent episodes.

It is impossible to predict individually, with any measure of precision, when another episode will occur or whether it will be manic or depressive. Of course, if a patient has a history of three previous depressive episodes, the diagnosis will be unipolar depression, and it is unlikely that a shift to bipolar disorder will occur later with the appearance of a manic episode, although the chance of such an error has been estimated to be about 10 percent. The author has seen one male patient, who, from the age of 21 throughout most of his life had an unbroken chain of 19 manic episodes until, at the age of 62, he started to suffer also from recurrent depressions and required a change of diagnosis to bipolar. In most cases it is justified to estimate, from a patient's individual history, the probable length of the free interval and the duration of the next episode, both of which tend to remain relatively stable.

Clinical experience and retrospective studies have established that with increasing age the intervals between episodes will shorten and both the frequency and duration of episodes will increase. One extensive long-term study has found that the number of episodes, while increasing in frequency for the first one or two decades, eventually tends to reach a "ceiling" level at about 10 episodes.

Bipolar patients generally have shorter cycles; that is, periods from the beginning of one episode to the beginning of the next, and thus more frequent relapses. In rare cases, "rapid cyclers" may change from depressions to manic states, or simply from one depressed or manic episode to a recurrence

of the same type, within weeks or days. It is well established clinically that the older a patient is at the onset of an affective disorder the sooner the next episode will occur. In young patients it is not unusual to have free intervals of 10 or even 20 years between the first and second episode. After all symptoms of an episode have disappeared with treatment, the following 3 months seem to be the most critical for a relapse.

Suicide A tragic, but not uncommon, outcome of depressive disorders is suicide. The danger of suicide is ever present in all depressed patients. Various studies indicate that suicide may occur in the setting of any psychiatric disorder and that more than 90 percent of all suicides are associated with some psychotic illness. Only 5 to 7 percent of suicides are of the "normal" or "rational" type. Close to 50 percent of all suicides are committed by depressed patients. An overview of 17 studies concludes that the risk among patients with primary affective disorders is over 30 times greater than in the general population and that the ultimate, lifetime risk of suicide in these disorders is about 15 percent.

Follow-up studies indicate that the annual rate of suicides in a population of patients diagnosed as suffering from affective disorders is about 1 percent. Special risk factors have been discussed under the Phenomenology heading of this section, but times of increased risk for suicide of depressed patients include the periods close to recovery and during the 2 years following a suicidal attempt.

For each completed suicide there are many more—at least 10—attempts that may be interpreted as "cries for help." Female and young patients make more attempts; male and old patients complete more suicides. One out of three or four who attempt suicide has a history of previous attempts. A strange and alarming rise of suicidal attempts and suicides has been observed over the last two decades among children—sometimes at preschool age—and adolescents in whom, after traffic accidents, suicide is today the most important cause of death. The reasons for this trend are not yet clear.

Mortality Mortality among patients with affective disorders was considerably higher than in the general population before the introduction of antidepressant and lithium therapy. Today it is still elevated, but is much lower than in the past. Many suicides today are avoided with earlier diagnosis and modern treatment, and many deaths are prevented. Formerly, significant numbers of deaths were associated with prolonged depressions, due to reduced resistance and intercurrent diseases, and with uncontrolled manic excitement caused by exhaustion or myocardial infarct—not uncommon complications in the past in depressed or manic patients of advanced age.

Chronicity An episode of affective disorder, depressive or manic, with a duration of more than 2 years may be defined as chronic. Such chronic conditions may last longer than 10 years and still end in recovery. If a chronic episode is not continuous but interrupted by short periods of days or weeks when the patient feels and behaves in a comparatively normal way, clinicians speak of intermittent chronicity.

Before effective treatment for affective disorders was available, the wards of mental hospitals housed many chronic depressed and manic patients. It was often difficult to distinguish a chronic depressive patient who was emaciated, sitting hunched over, motionless and mute, in a depressive stupor, from a severely demented patient or a backward schizophrenic patient, until one day the chronic depressive patient would suddenly and unexplainably start to recover rapidly—perhaps 9 or 10 years after admission to the hospital. Today these extreme cases are no longer seen, but approximately 15 percent of depressed patients will still become chronic. They are the treatment-resistant patients who are frequent visitors to outpatient clinics.

The following features were found to be associated with above-average duration of affective disorder episodes before the availability of effective treatment: (1) hereditary loading; (2) over 50 years of age; (3) complicating neurotic components; and (4) associated physical illness, particularly organic brain disease.

Many clinicians today consider depressions with hypochondriacal symptoms as being difficult to treat, whereas others observe that often the less intense depressions tend to develop a chronic course. An unfavorable early environment, e.g. having been raised in a broken home, also predisposes to poorer response to treatment.

"Double depression" Patients whose endogenous, acute, depressive episode is superimposed on a preexisting neurotic depression, a dysthymic disorder, or a depressive personality structure—a "double depression" as it has been described—are more likely to develop treatment-resistant, chronic depressions.

Age Elderly patients also frequently develop chronic depressions, possibly because of early organic brain pathology or the increased stress load and reduced capacity to adapt. That old age by itself does not necessarily preclude response to antidepressant therapy is illustrated by the case report of a manic-depressive women who died at the age of 103 years.

> The woman had suffered numerous episodes of depression beginning at the age of 7 and had responded to ECT and antidepressant pharmacotherapy between the age of 75 and 95, at which time confusion and an organic brain syndrome supervened. During the last 8 years of her life, she remained almost continually depressed. On autopsy, senile deterioration but no evidence of arteriosclerosis was found in the brain.

Alcoholism Another type of therapy-resistant depression may be found among depressed patients who also are alcoholics. Coexistent alcoholism renders many depressed patients inaccessible to effective antidepressant pharmacotherapy because of the potential complications caused by the interaction of large doses of alcohol with antidepressant drugs. For depressed alcoholics to stop drinking while receiving antidepressant treatment is unfortunately the exception rather than the rule because most patients feel compelled to cling to the instant antidepressant effects of alcohol and will not wait for the delayed effects of antidepressant drugs.

The continued use of alcohol may also be overdetermined, in that it not only provides immediate relief but also is an effective means of eventual self-destruction that the depressed patient may be seeking consciously or unconsciously. Similar problems are frequently encountered when depressed patients are drug-dependent.

Insoluble problems Still another group of depressed patients often fails to respond to all therapeutic efforts because they are facing intolerable ongoing stresses and problems for which neither they nor others can find any solution. This dilemma may apply to such existential contingencies as old age, loss of personal status, chronic disease, infirmity, and loneliness.

Overwhelming traumatization The specific etiology of their depressions may be the reason why certain depressed patients fail to respond to any treatment. Included in this group, for example, are many survivors of Hitler's horror concentration

camps who may be suffering from the aftermath of a new type of reactive depression—sometimes referred to as the survivor's syndrome—that, in contrast to most other reactive depressions, is chronic and often irreversible. Its characteristic symptoms are tension, irritability, constant apprehension, somatic and sleep disorders, recurrent nightmares, a severe restriction of interests, and an all-pervasive anhedonia.

Treatment-related factors Finally, in many cases, the apparent resistance to treatment of some affective disorders can be explained by factors related to the treatment itself. The diagnosis may have been missed and no appropriate treatment prescribed. Also the prescribed treatment may have been inadequate—for instance insufficient doses for too short a time—or more frequently, the patient, overtly or covertly, refused to comply with therapy. Fortunately, this situation can, more easily than the other ones, be successfully modified to improve the outcome of an affective disorder that has failed to respond to treatment and threatens to become chronic.

INFLUENCE OF HISTORY AND CULTURE ON SYMPTOMS

Have the symptoms of the affective disorders changed over the years? What are the differences in the way the symptoms are manifested in different cultures in the world today?

Historical changes Descriptions of depression have been found in ancient Egyptian odes and poems preserved on papyri.

To be suffering from melancholia was considered almost a status symbol in certain cultural settings of the 17th and 18th century. Burton, a clergyman, and himself a sufferer from morbid depression, wrote the first classical treatise on depression, *The Anatomy of Melancholy*, in 1621 (Fig. 18.5–9).

During the romantic literary period in Western Europe, particularly in 18th- and 19th-century Germany, existential despair or *Weltschmerz* reached almost epidemic proportions and led to a wave of suicides in the wake of Goethe's publication of the "Sufferings of Werther."

Systematic research into the changes in depressive symptomatology during the last century has determined that in the Western Judeo-Christian sphere of civilization there has been a notable decrease of guilt feelings, particularly in relation to transcendental or religious issues. It is estimated that guilt feelings, which used to be characteristic of endogenous depression in 70 to 75 percent of all cases, now occur in only 30 to 40 percent of cases. Instead of moral guilt feelings, there has been a clear increase in feelings of personal inadequacy. Similarly, the type of anxiety that used to characterize morbid depressions in the 19th century, i.e. anxiety about the end of the world or the destruction of civilization of one's country, is now replaced by anxiety about one's own individual existence.

One clinician has commented on the "de-dramatization" of depression in society over the past half century. Whereas old and, at the time, apparently typical accounts of depression spoke of depressive delusions—for instance, having one's heart turned into stone, having one's intestines blocked completely, having committed an unpardonable sin—today's depressive patient is more likely to speak of occupational inadequacy, inadvisable investments, irresponsibly poor judgment.

The frequency of hypochondriacal symptoms in depression, symptoms that are present in approximately 25 percent of

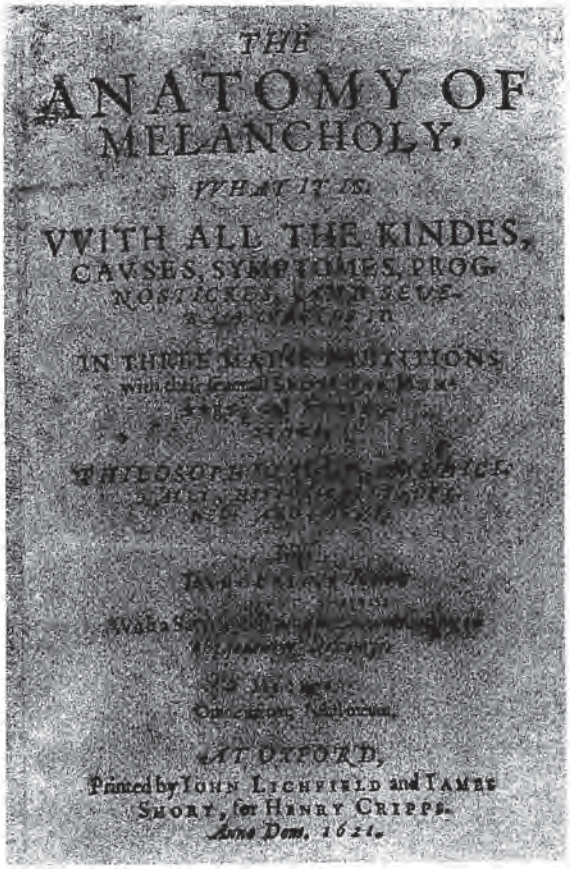
THE
ANATOMY OF
MELANCHOLY,
WHAT IT IS.
WITH ALL THE KINDES,
CAVSES, SYMPTOMES, PROG-
NOSTICKES, AND SEVE-
RALL CVRES OF IT.
IN THREE PARTITIONS,
AT OXFORD,
Printed by IOHN LICHFIELD and IAMES
SHORT, for HENRY CRIPPS.
Anno Dom. 1621.

FIGURE 18.5–9. *The title page of Robert Burton's (1577–1640)* Anatomy of Melancholy, *published under a pseudonym. Note the inclusion of a "Satyricall Preface." (Courtesy of Osler Library, McGill University, Montreal.)*

today's depressions in industrialized countries, has not changed over the years.

Similarly, the frequency of suicidal tendencies, which are present in at least 70 percent of all depressive conditions, probably has not changed over the years, although the incidence of completed suicides changes—sometimes dramatically—from decade to decade and seems to be clearly related to cultural, economic, political, and other situational swings.

In Soviet Russia, an increase of pseudodementia syndromes in depressed patients has been observed in the decade between 1961 and 1971, and at the same time, an increase in atypical depressions and a increase of delusional symptoms in depression. During the 1960s, the depressive affect was more frequently expressed as "gloomy irritation" in Russia. Also, during the period between 1950 to 1971 in Russia, there was a tendency toward shorter duration and more favorable outcomes of depressive episodes, which was probably related to better treatment methods.

Cultural differences When comparing depressive symptoms across various cultures, one general difference has been noted between industrialized and developing countries and between Christian and non-Christian cultures.

In developing countries, depressed patients complain mainly of somatic and functional symptoms, such as pain, indigestion, insomnia, constipation, weight loss, sexual dys-

function, and lack of energy, probably reflecting their (primitive) image of the sick role. Many of these patients also express paranoid delusions. They complain relatively less often of a differentiated depressive mood or guilt feelings. They seldom commit suicide.

The presence of guilt feelings seems to be significantly related to the Judeo-Christian religion, which may have a pathoplastic influence on the formation of depressive symptoms. Many independent investigators have reported that guilt feelings and concerns over having sinned are virtually absent in depressed people in Africa and India. One psychiatrist has reported that a man from India who was suffering from periodically recurrent depressions did not suffer any guilt feelings until he was converted to Christianity. Some studies from Egypt suggest that feelings of personal guilt in the Moslem culture are as frequent as in the Judeo-Christian culture. Furthermore, common situational causes for chronicity of depression among women in the Arab culture are (1) to remain unmarried or (2) to remain childless.

In general, a well-trained psychiatrist would probably be able to arrive at an accurate diagnosis of a depressive state in any culture, because there are sufficient common features that override specific differences in symptomatology. In a recent study sponsored by the World Health Organization (WHO), a sample of 573 depressed patients was derived from four different countries—Canada (Montreal), Iran (Teheran), Japan (Nagasaki; Tokyo), and Switzerland (Basle)—to test the applicability of a uniform diagnostic instrument, the WHO/SADD, in these four different cultures and to determine whether there were any fundamental differences in the phenomenology of depression. The findings, based on computer analysis of the clinical data and a comparison of sound-film recordings of depressed patients in the four countries, established that there were no important differences in the symptomatology of depression between the different samples and that the same diagnostic instrument could be employed in all the four countries.

Depression in Africa Much has been written about depression in Africa, but there is still no general agreement about the prevalence and the symptomatology of depression on that continent. Kraepelin reported that depressive episodes among African natives often begin with states of excitement and aggression and then change into depressive states. There is a general agreement that somatic symptoms play a prominent role in all depressions in non-Western countries. Examples of common complaints made by African depressives are of "heat in the brain" or "worms crawling all over the head."

Delusions of persecution are frequent, occurring in close to one-third of all depressed patients. The paranoid ideas usually involve envious neighbors or co-workers or jealous rivals. Guilt feelings are less often observed than in the depressives of the Western world, but if they are present they are frequently ascribed to failure of having served the ancestors according to custom. The general belief among natives that mental illness is caused by supernatural forces, mainly bewitchment, frees depressed persons from all personal responsibility for their suffering.

For those depressed Africans who blame their miserable state on witches and spirit forces of their ancestors, the prognosis is poor, and their illness frequently lasts for years. In one recent follow-up study, only 16 percent of depressed patients at an African outpatient clinic became symptom-free, and 26 percent showed modest improvement. That left 58 percent with little or no improvement.

Suicide in African countries is very rare, probably less than 1 in 100,000, and if it occurs it is almost always an impulsive act, seldom premeditated. As in the developed countries, an ominous rise of suicidal attempts has been observed in the younger age groups in Africa.

Manic patients in Nigeria showed all the common symptoms of this syndrome, except flight of ideas, which was rarely observed in this cultural setting.

Culture and depression in Japan In Japan the special uniformity of its culture, which has not been disturbed by massive immigration, ethnic division, or language differences, has shaped what is called a "cohesive character" in many of its inhabitants. One survey revealed that 40 percent of male students at a university were of this type. Features of this character are conscientiousness, meticulousness, perfectionism, and persistence. Lack of formality and rigidity differentiate it from the typical obsessive-compulsive personality. The cohesive character resembles the German *typus melancholicus* and seems to have a significant influence on the symptoms of the depression to which it often predisposes. One study found that more than 90 percent of a group of depressed patients in Japan had the cohesive character structure that is particularly sensitive to changes in the environment, tradition, and social structure and results in strong feelings of obligations toward the group.

Depression among the Amish An interesting recent study among the Amish, a religious rural community in Pennsylvania, established that, contrary to the traditional preponderance of women among depressed patients, with a ratio usually reported at 2:1 or 3:1, among the Amish the occurrence of unipolar depression was equally distributed among men and women. Among their bipolar patients, there was a higher frequency for men. One of the reasons given for this deviation from the usual findings is that alcoholism and sociopathy do not exist among the Amish and therefore cannot mask the diagnosis of depression or be equivalents for depression in men, as is often the case in other cultures. Another theory holds that, among the Amish, women cannot adopt a sick or neurasthenic role any more than men, because their dominant work ethic requires all women to be visibly working and functioning at a high level just as men are.

Comparative studies In the WHO study across four cultures, a set of eight "core" features of depression was present in 76 percent of all patients in the study: sadness, joylessness, anxiety, tension, lack of energy, loss of interest, impaired concentration, and ideas of inadequacy. Suicidal ideas were observed in close to 60 percent of all patients combined, but were less frequent in Tokyo and Teheran. Feelings of guilt and self-reproach were most frequent in Basle and Montreal (68 and 58 percent) and least frequent in Teheran (32 percent). Somatic symptoms were most prevalent in Teheran (57 percent) and least prevalent in Basle (32 percent) and Montreal (27 percent). Psychomotor agitation had a combined frequency of 42 percent, but Teheran had by far the highest frequency with 64 percent.

A study in which Southern Italian and Swedish depressed patients were rated for various symptoms found that the Italians scored higher on motor retardation, loss of interest, hopelessness, and hypochondriasis, whereas the Swedes rated higher on agitation and inability to feel.

A comparison of depressive symptoms in Egyptian and British patients revealed that somatic symptoms and anxiety were significantly more frequent among the Egyptian patients, whereas guilt, insomnia, and hypochondriasis were more

frequent among the British. Agitation, too, was more frequently observed in British depressives. Hypochondriasis, anxiety, and agitation have been observed more frequently in patients from India than from Britain, whereas the reverse is true for obsessional symptoms.

When comparing Egyptian with Indian depressives, it appeared that insomnia, retardation, agitation, hypochondriasis, and diurnal variation were significantly more frequent in the Indian sample. The difference was especially marked in agitation, which was 8 times more frequent in the Indian sample than in the Egyptian sample.

Even within the same city, different language groups may show great differences in the frequency of specific symptoms in depressed patients, as illustrated by the fact that, in one study, French-Canadian depressives in Montreal reported no difficulty in thinking or expressing themselves, whereas 45 percent of depressed Canadians of British origin reported this symptom. Only 15 percent of the Anglo-Canadians reported numerous somatic troubles, whereas 60 percent of the French Canadian depressives reported somatic complaints.

SUGGESTED CROSS REFERENCES

Other sections in this chapter deal with the epidemiology, biochemistry, and genetics of affective disorders. Schizoaffective disorders are covered in Chapter 17. An overview of organic mental disorders is discussed in Chapter 19. Suicide is covered in Section 28.1. Postpartum disorders are found in Section 26.2. Grief, mourning, and bereavement are covered in Section 27.3. For a thorough discussion of drugs used treating depression, see Section 30.2.

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18.6 AFFECTIVE DISORDERS: PSYCHOSOCIAL TREATMENT

ROBERT M. A. HIRSCHFELD, M.D.
M. TRACIE SHEA, Ph.D.

INTRODUCTION

Great strides have been made over the past decade in our understanding of the psychotherapy of depression. This progress has resulted primarily from theoretical advances in the psychology of depression, which in turn were influenced by developments in the classification of psychiatric disorders and in psychopharmacology.

The principal development in psychiatric classification has been a shift toward the use of manifest psychopathology, i.e. signs and symptoms, as the unit of classification. Although this is not a new idea, the most prevalent approaches to diagnosis in the past have been based on inferences about unconscious processes or on a unitary theory of mental disorders. Agreement among clinical raters, i.e. reliability, is vastly easier to achieve using the current approach, and the development of operational criteria for diagnostic categories has been a parallel process. These categories may be tested for usefulness in terms of increased communication, etiology, selection of treatment response, and prediction of clinical course.

The discovery of selective therapeutic effectiveness of particular medications for specific conditions has gone hand-in-hand with the nosological advances. First were the phenothiazines for schizophrenia; the monoamine oxidase inhibitors and tricyclic antidepressants followed for depression, and lithium for mania. This selectivity of therapeutic response provides a clear clinical rationale for use of nosology in practice.

Developments in psychotherapy have been influenced by these two movements. Psychotherapeutic approaches that aim at correction of specific aspects of depression, including cognitions, behavior, and affect, have been developed specifically for the condition of depression. In general they are short term and seek to alleviate the depressive condition per se, not to change character.

This section of Chapter 18 will describe those psychotherapies that have been developed specifically for the treatment of depression or that have direct relevance to treatment of depression, such as short-term psychodynamic therapies, interpersonal therapy, behavioral therapies, cognitive behavioral therapy, and family and marital approaches that are geared to depression.

For each of these therapies, the historical roots and the specific theoretical model of depression unique to that approach will be briefly reviewed. General characteristics of the approach will then be discussed, followed by a description of specific techniques and strategies employed in the therapy. The efficacy data that exist will also be described.

PSYCHOANALYSIS AND PSYCHOANALYTIC APPROACHES

THEORETICAL ROOTS AND THE CONCEPT OF DEPRESSION As comprehensive review is well beyond the scope of this section, a brief focused review follows for the purpose of introducing psychoanalytic principles to the treatment of depression.

The interpersonal nature of depression was noted and emphasized in even the earliest psychoanalytic writings on depression, as was the centrality of the regulation of self-esteem. In *Mourning and Melancholia*, Freud described that a vulnerability to depression caused by an interpersonal disappointment very early in life led to future love relationships marked by ambivalence. Actual or threatened interpersonal losses in adult life would trigger a self-destructive struggle in the ego that would be manifested as depression.

This theory was significantly refined by other psychoanalysts who formulated a description of the depression-prone personality as one needing constant reassurance, love, and admiration. Such individuals are inordinately dependent on others for narcissistic gratification and for maintenance of self-esteem. Frustration of their dependency needs leads to a plummet in self-esteem and to subsequent depression. Later, this notion was expanded to include any individual with a fragile self-esteem system.

Another dynamic approach focused on cognitive aspects, highlighting a recognition of the disparity between one's actual and idealized situation. This realization leads to a sense of helplessness and powerlessness and, subsequently, to depression.

Common to all psychoanalytic contributions is a disturbance in interpersonal relations in early childhood, usually involving a loss or disappointment. This experience impairs subsequent interpersonal relations and renders the individual especially vulnerable to interpersonal disappointments and loss later in life.

GOALS In general, the goal of psychoanalytic psychotherapy is to effect a change in personality structure or character, and not simply to alleviate symptoms. Improvement in interpersonal trust, in intimacy and generativity, in coping mechanisms, in ability to experience a wide range of emotions, and in the capacity to grieve are some of the aims. Treatment may often require the patient to experience heightened anxiety and distress during the course of therapy, which usually continues for several years.

Several approaches that are based on psychoanalytic principles have recently been developed and have been used in the treatment of depression. They seek to reduce symptomatology, resolve neuroses, and improve the quality of life.

GENERAL CONSIDERATIONS Early psychoanalytic treatments were short in duration in comparison with those of current practice, usually lasting no more than a few months. Freud, for example, cured Gustav Mahler, the composer, of a sexual problem in one 4-hour session. Psychoanalytic treatments lengthened in duration as development and interpretation of the transference relationships became the core of the therapy and as the therapists became more passive in their behavior.

Several clinicians, including Franz Alexander in Chicago, attempted to reverse this trend, but over all, they have had relatively little impact on their colleagues. In the last 2 decades, however, several specific short-term psychoanalytic approaches have been developed that are applicable to the treatment of depression. Perhaps the most seminal work was by Michael Balint and his colleagues in the 1950s at the Tavistock Clinic in London. The work has been continued by David Malan following Balint's death. Other contributors include Habib Davanloo in Montreal, Peter Sifneos in Boston, and Hans Strupp in Tennessee (Table 18.6–1).

These therapies are all psychoanalytic in theory and practice, and they utilize the transference relationship as the key to treatment. The patient-therapist relationship is used to examine and reexperience important past relationships that may account for current difficulties. All involve active participation by the therapist and discourage free association techniques. Identification and emphasis on a single focal issue is another common feature.

Identification of suitable patients for these short-term psychoanalytic therapies is given preeminence by all proponents. In general, the patient selection criteria are very similar, although some differences exist among the therapies. Psychological-mindedness and intelligence are considered to be very important; individuals should be capable of introspection and should be able to see a connection between thoughts, feelings, and behavior. A strong motivation for change should exist in connection with flexibility; this motivation may be tested by assessing the patient's responsiveness to interpretations early in therapy. A capacity for meaningful human relationships must have been demonstrated at some time during life. Finally, the capacity to tolerate anxiety and frustration is required. Obviously these criteria result in the exclusion of a significant proportion of psychiatric patients, leaving only the

TABLE 18.6–1
Features of Short-term Psychoanalytic Approaches

Name	*Duration of Treatment (No. of Sessions)*	*Specific Time Limit*	*Indications*	*Special Notes*
Brief psychotherapy (Malan)	20–40	Yes	Any patient with a focal life problem who responds to interpretations	Interpretations emphasize early parent-child relationships
Short-term dynamic psychotherapy (Davanloo)	15–30	No	Oedipal problems Neurotic problems where the focus is loss Obsessional and phobic neuroses Long-standing characterological problems without a single focus	Highly confrontational Recommended for very resistant patients Not recommended for patients with significant dependency or separation problems
Short-term anxiety-provoking psychotherapy (Sifneos)	12–15	No	Oedipal "triangular" interpersonal problems	Avoids regression into pregenital characterological issues
Time-limited dynamic psychotherapy (Strupp)	less than 25	Yes	Avoidant, dependent, compulsive, and passive-aggressive personality disorder associated with depression, anxiety, and resentment	Focus on interpersonal themes

most desirable, verbal therapy candidates. The proponents of these therapies point out, nonetheless, that true character change is achieved in a relatively short time and that serious personality problems are addressed.

STRATEGIES AND TECHNIQUES Among the specific techniques used in these approaches are active interpretation of the transference, identification of and emphasis on a specific dynamic focus, active collaboration between the patient and therapist, and discouragement of regression.

The *transference relationship* is the heart of the short-term psychoanalytic approaches. The therapeutic relationship is composed of two aspects, the real and the transferred. The real relationship refers to thoughts, feelings, and behaviors that are relevant to and appropriate for the current interaction between patient and therapist. The transferred aspect is used to identify and reexperience problems and patterns that developed in important relationships early in life. This process is considered to be the key for all psychoanalytic approaches. In the short-term approaches, development and interpretation of the transference are actively pursued, often right from the outset. This approach is illustrated in an excerpt from an initial session with Davanloo where the patient's passivity is immediately challenged.

Therapist: How do you feel about talking to me about yourself?
Patient: I feel uncomfortable. I have never done this before, so I don't really, you know.... I feel I don't really know how to answer some of your questions.
Therapist: Um-hum. But have you noticed that in your relationship here with me you are passive, and I am the one who has to question you repeatedly?
Patient: No.
Therapist: Um-hum. What do you think about this? Is this the way it is with other people, or is it only here with me? ... This passivity, lack of spontaneity.

A vignette from an initial session with Sifneos illustrates another way in which active and direct interpretation of the transference occurs.

Patient: I put on an act. I wear a mask. I give the impression that I'm different from what I really am. I don't like this attitude in me.
Therapist: Can you give me an example?
Patient: What happened last week is a case in point. Before my girlfriend broke off our relationship, she said that she didn't like going out with someone who is a phoney. ... Mary, my previous girlfriend, had said the same thing, using different words, and so did Bob, my best friend. I know what they are all talking about. At times, even here, I have this great urge to show off and make you admire me.
Therapist: And where does this urge come from?
Patient: From very long ago. I used to put on an act to impress my mother. I remember one time when I made up a whole story about school. I told her that the teacher had said I was the best student she had ever had. My mother was impressed, but you know, doctor, it wasn't true. The teacher had complimented me, but I exaggerated it. I blew it out of proportion.
Therapist: So you were trying to impress your mother, you are trying to impress your girlfriends and Bob, and even here ....
Patient: What do you mean by even here?
Therapist: A minute ago you said that even here you had such a tendency.
Patient: Did I say that?
Therapist: Yes you did. Furthermore, why does it surprise you? If you put on an act with everyone else, why couldn't you put on an act with me?

The short-term therapies differ from classical psychoanalysis in their emphasis on the identification of a specific *dynamic focus.* A particular issue, usually an interpersonal problem, is selected, and both the patient and therapist agree to deal primarily with this problem during therapy. This focus is considered dynamic because it is used as a link with core conflicts arising from early life. This technique actively uses the current conflict as a microcosm for the more substantial and long-lasting conflicts in the patient's life.

In his manual, Strupp describes a married woman in her thirties who sought treatment for recurrent depressive episodes.

The woman's manner in the interview was somewhat aloof and curt, which led the therapist to wish to discuss facts, rather than to elicit feelings. When this inclination was pointed out to her, the patient responded that she could not imagine that anything she said could be of interest to anyone, and therefore, she acted in this way to protect herself from being hurt. The dynamic focus then became an exploration of her expectation that she was of no interest to anyone. A link was subsequently made with the patient's childhood, during which her parents seemed to prefer her sisters to her.

Active collaboration between the patient and therapist involves the establishment of a working alliance. The therapist seeks to convey interest in the patient's problems, as well as respect and warmth. There is an attempt to elucidate explanations by the patient, in addition to using interpretations. Thus a mutuality and common purpose are fostered.

Although not common to all the short-term psychoanalytic approaches, most discourage regression. The principal reason for this is that emergence of such material as pregenital characterological issues often leads to significant therapeutic impasses that may not be resolved in a short period of time. Sifneos gives an example of a patient who became very angry and demanding about the make-up of a cancelled session. Instead of encouraging associations to childhood orality and dependency, the therapist confronted the maladaptive and self-destructive current behavior of the patient and encouraged the patient to request an extra session, rather than being angry and withdrawn.

EFFICACY Unfortunately, efficacy data on short-term psychoanalytic approaches to the treatment of depression are almost nonexistent. No studies have been reported that test a specific approach against appropriate control groups, in which patients meeting criteria for major depressive episode in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) were used and independent outcome evaluation was included. Part of the reason for this omission is that the developers of these strategies emphasize psychoanalytic concepts, rather than empirical diagnostic categories.

INTERPERSONAL THERAPY

THEORETICAL FOUNDATIONS AND CONCEPT OF DEPRESSION Interpersonal Therapy (IPT) was developed by Gerald Klerman and Myrna Weissman as part of their extensive research on the nature and treatment of depression over the last two decades. The theoretical basis of IPT includes the work of Adolf Meyer and Harry Stack Sullivan. In contrast to the predominantly intrapsychic orientation of classical psychoanalysis and to the biomedical model of Kraepelin, the psychobiological approach of Meyer emphasized the interaction between the individual and the psychosocial environment over the whole life course. The patient's current interpersonal experiences and attempts to adapt to environmental change and stress were seen as critical factors in psychiatric illness. Sullivan's interpersonal theory viewed interactions between people as the focus for study and treatment in psychiatry. His theory drew heavily from the social sciences, including anthropology and sociology.

A second major influence came from Bowlby's studies of attachment. These studies demonstrated the importance of attachment and social bonding to human functioning, and the connection between disruption of these bonds and vulnerability to depression.

In IPT depression is conceptualized from a medical model vantage. Thus, depression is viewed as something that happens to the individual and that requires treatment. The depressed person can then assume the sick role and not be blamed for the affliction any more than someone would be blamed for having cancer, heart disease, or pneumonia. This issue of attribution of blame is an important one. In many other approaches, depression is viewed as something brought on by oneself and as something of which individuals must rid themselves.

The IPT approach to depression involves three interacting components: symptom formation, social and interpersonal experiences, and enduring personality patterns. In IPT, medication is often recommended for reduction of symptoms, and psychotherapy is focused on improvement in the patient's interpersonal life. Although etiology may vary with regard to biological vulnerability or personality predispositions, depression always occurs in a psychosocial and interpersonal context. Depression can predispose the patient to interpersonal problems, or interpersonal problems can precipitate depression. An interpersonal focus in the treatment process is thus presumed essential for symptom recovery.

GOALS The first of IPT's two goals is to reduce depressive symptoms and to improve self-esteem. The second is to help the patient to develop more effective strategies for dealing with social and interpersonal relations. As a short-term psychotherapy, there is no attempt to restructure the patient's character. The importance of early developmental experiences is recognized, but the emphasis is on interpersonal relationships in the current life situation, as it is assumed that the historical conflicts will be manifested in the current relationships.

GENERAL CONSIDERATIONS IPT is a short-term psychotherapy, normally consisting of anywhere from 12 to 16 weekly sessions, and it was developed specifically for the treatment of nonbipolar, nonpsychotic ambulatory depressives. It is characterized by an active approach on the part of the therapist and by an emphasis on current issues and social functioning in the life of the patient. Intrapsychic phenomena, such as defense mechanisms or internal conflicts, are not addressed in the therapy. Discrete behaviors, such as lack of assertiveness, social skills, or distorted thinking, may be addressed, but only in the context of their meaning or effect on interpersonal relationships.

STRATEGIES AND TECHNIQUES **General strategies** General strategies are described for each of the two primary goals. For the reduction of symptoms, an educational approach is employed. The patient is informed about the nature of the clinical syndrome of depression, including its components and course. The therapist reviews symptoms with the patient and, in an attempt to instill the patient with a sense of optimism and hope, emphasizes the fact that depression is a common disorder with a good prognosis. Pharmacotherapy may be considered for use in conjunction with IPT if deemed appropriate.

The general strategy for the second goal, helping the patient to deal more effectively with current interpersonal problems, involves establishing a problem area from the patient's interpersonal issues. IPT defines four major problem areas that are commonly presented by depressed patients and outlines associated therapeutic goals and recommended treatment strategies for each. The areas are (1) grief, (2) interpersonal disputes, (3) role transitions, and (4) interpersonal deficits (Table 18.6–2). Definition of a problem area helps the therapist to outline realistic goals and productive treatment strategies, because the choice of specific IPT strategies and techniques will depend on the problem area defined as most salient for the patient. The problem areas are not mutually exclusive, and patients may have multiple problems in more than one area; however, only one or two current interpersonal problems within the four areas are selected for focus in the therapy.

Cases of abnormal grief may involve delayed or distorted mourning or both. For example, as cited in the IPT Manual:

> A 68-year-old woman became depressed following the death of her husband who had suffered a long course of physical and mental deterioration, which resulted in considerable constraints and isolation on the part of the patient. Her symptoms included pervasive sadness and preoccupation with feelings of guilt and hopelessness. The first aim of treatment was to help the patient to successfully mourn the loss, as the mourning process had been blocked by anger. The second aim was to help her to reestablish interests and relationships to substitute for what she had lost.

Interpersonal issues involved in a troublesome and conflicted marriage may be examples of role disputes or role transitions. The choice between the two problem areas will depend on the patient's conviction as to whether the marriage is salvageable and on that person's desire to stay in the marriage or to leave. If the patient decides to leave the marriage and the problem area is defined as role transition, the therapist will attempt to help the patient to make the

TABLE 18.6–2
Interpersonal Problem Areas

Problem Areas	*Definition*	*General Goals and Strategies*
Grief	Abnormal grief reactions resulting from failure to go through normal mourning following the death of a person important to the patient	Facilitate the mourning process Help patient reestablish interests and relationships to substitute for the ones lost
Interpersonal disputes	Patient and significant other(s) have nonreciprocal expectations about the relationship	Help patient identify the dispute Guide patient in choices as to plan of action Encourage modification of maladaptive communication patterns Encourage reassessment of expectations
Role transitions	Patient feels unable to cope with change in life role, which may be experienced as threatening to self-esteem or sense of identity or both	Help patient to regard role in a more positive and less restrictive manner Restore self-esteem by helping patient to develop sense of mastery with regard to demands of new role
Interpersonal deficits	Patient has history of inadequate or unsustaining interpersonal relationships	Reduce patient's social isolation by focusing on past relationships and relationship with therapist and by helping patient to form new relationships

transition. This may include working on identification of new sources of emotional support, helping the patient to overcome irrational fears and to regard the new role more positively, and helping the patient to master the demands of the new role. Alternatively, if the problem area is defined as a role dispute, treatment strategies will include identification of the dispute and working toward its resolution. Improving communication patterns, examining appropriateness of expectations, outlining various options, and deciding a plan of action will be employed.

The interpersonal deficit problem area is appropriate for patients who are socially isolated or have an appropriate number of relationships but feel unable to enjoy them. Interpersonal deficits may exist in patients who are chronically depressed, resulting in impaired interpersonal functioning. Problems with social isolation may be long-standing or temporary; treatment strategies are geared toward reducing social isolation. In the absence of current relationships, discussion of positive and negative features of past relationships may be used to provide a model for the development of new relationships. Treatment may also focus on the relationship between the therapist and the patient.

An example of an interpersonal deficit cited by the IPT Manual is as follows:

> A 22-year-old single male became severely depressed 1 month after the breakup of a 3-year relationship with his girlfriend. The patient, a part-time student employed as a cook, lived with his mother, who had stopped working after being hospitalized for physical problems, and subsequently, he had become depressed. Discussion of the patient's current relationships revealed that, apart from his mother, he felt close to no one.
>
> Information from the patient's past revealed a history of inadequate social relationships and lack of interpersonal skills. The treatment focused on past significant relationships and on his conflicts over his relationship with his mother. The patient-therapist relationship provided a direct source of information about the patient's style of relating to others, and this information was used to modify maladaptive interpersonal patterns.

Specific techniques The specific techniques employed in IPT may be used in any of the four interpersonal problem areas. In the general order of their use in the course of treatment, they include (1) exploratory techniques, (2) encouragement of affect, (3) clarification, (4) communication analysis, (5) use of therapeutic relationship, and (6) behavior change techniques (Table 18.6–3).

TABLE 18.6–3
Interpersonal Therapy Techniques

Techniques	*Definition*
Exploratory techniques	Collection of information about patient's symptoms and problems, which can be directive or nondirective.
Encouragement of affect	Help patient to recognize and accept painful affects Help patient to use and manage affects positively in interpersonal relationships Encourage expression of suppressed affects
Clarification	Restructure and feed back patient's communications
Communication analysis	Identify maladaptive communication patterns Help patient to communicate more effectively
Use of therapeutic relationship	Examine patient's feelings and behavior in therapeutic relationship as a model of patient's interactions in other relationships
Behavior change techniques	Use of techniques to help patient solve simple life problems Teach patient to consider range of options for solving problems Use role playing to explore and understand patient's relationship with others and to train patient in new ways of interacting with others.

In summary, IPT places interpersonal issues in a preeminent position in the depressive syndrome, either as a cause or as a complication, which, as such, need to be addressed in the treatment of depression. In IPT a formulation of the patient's predominant interpersonal problems is made in terms of an interpersonal problem area, which defines the focus for treatment and guides the subsequent choice of therapeutic strategies and techniques employed throughout the course of treatment.

EFFICACY DATA Two controlled clinical trials—an acute treatment study with depressed men and women, and a maintenance treatment study with recovering depressed women—have shown IPT to be superior to a no active treatment control group. Both studies also demonstrated that IPT in combination with amitriptyline was more effective than either treatment alone. In the maintenance study, IPT was found to enhance social functioning in patients who completed 8 months of treatment and did not relapse.

BEHAVIORAL APPROACHES

THEORETICAL ROOTS AND CONCEPT OF DEPRESSION Although current behavioral approaches to depression are somewhat divergent in their theoretical assumptions and specific treatment methods, they have a clear common source. Skinner, incorporating the principles of classical conditioning and, more importantly, operant conditioning in an empirical analysis of behavior, provided the basic framework, methodology, and assumptions for current behavioral theories and their clinical applications.

The application of the behavioral model to complex human behavior led some theorists to expand the framework. For example, social learning theory includes cognitive phenomena in its emphasis on the role of subjective expectations and value in reinforcement. Nonetheless, the hallmarks of all behavioral therapies are (1) the links between an observable or operationally definable behavior and precise conditions that control or determine it, and (2) the role of rewards or reinforcement as determinants of behavior and behavioral change.

The introduction of the behavioral approach to depression occurred in 1965 with an analysis of depression by Ferster, who proposed that depression is caused by a loss of positive reinforcement. The loss of the usual supply of reinforcement may be due to such events as separation, death, or sudden environmental change, and this loss results in reduction of the entire behavioral repertoire, as well as depressed behaviors and dysphoric feelings. This concept of depression is central to all behavioral approaches. A change in the rate of reinforcement is believed to be a key factor in the origin, maintenance, and reversal of depression. This change may occur when there is a lack of available reinforcers or when the available reinforcers are not contingent on the person's behavior. Ferster also proposed that a social skills deficit, characterized by difficulty in obtaining social reinforcement, might make it more difficult to cope with the loss of the usual supply of reinforcement. The role of social skills deficits in depression is also common to many of the behavioral approaches.

GOALS The goals of the behavioral therapies are to increase the frequency of the patient's positively reinforcing interac-

tions with the environment and to decrease the number of negative interactions. Some of the behavioral treatments aim also at improvement of social skills. Alteration of personal behavior in depressed patients is believed to be the most effective way to change the associated depressed thoughts and feelings.

GENERAL CONSIDERATIONS Several behavior therapies have been developed for the treatment of depression, including Lewinsohn's social learning therapy, Rehm's self-control therapy, Hersen and Bellack's social skills training, and McLean's multimodal treatment package. Table 18.6–4 gives a summary of strategies and tactics associated with each approach. Although they vary in terms of specific techniques and focus, these therapies have certain assumptions and strategies in common:

1. The treatment program is highly structured and generally short-term.
2. The principle of reinforcement is seen as the key element in depression.
3. Changing behavior is considered to be the most effective way to alleviate depression.
4. The focus is on articulation and attainment of specific goals.

Some behavioral treatments are characterized by multicomponent treatment approaches combining a variety of behavioral techniques, where the use of techniques may be tailored to the individual needs of each patient. Normally there are core ingredients, considered essential, in conjunction with a number of optional techniques.

Strategies and techniques Although the major behavioral approaches to depression vary in their focus and emphasis in treatment and in frequency of use of specific techniques, there is considerable overlap. Detailed manuals have been written specifying treatment regimes for most of these approaches. Some of the salient behavioral techniques will be briefly described here.

Maintaining records Recording of mood and activities, both positive and negative, is an essential part of most behavioral therapies. Patients may also monitor immediate and longer-term consequences of specific behavior.

Increase general activity level, particularly pleasant events On the basis of the daily mood and activity recordings, the therapist encourages the patients to increase their participation in those activities rated as most pleasant, by demonstrating a relation-

TABLE 18.6–4
Behavioral Approaches to Depression

Treatment Approach	*Basic Approach and Strategies*	*Tactics*
Multimodal treatment (McLean)	Identify symptomatic areas, design specific behavioral strategy to deal with each problem. Six skill-deficit areas are assessed with pretreatment questionnaires. Three areas are treated in every patient (communication, behavioral productivity, social interaction); three areas are optional (assertiveness, decision making, problem solving)	Communication feedback training and practice Graduated performance assignments Give patient information about social environment in community Role playing Assertiveness training Relaxation training Cognitive techniques (Thought delay, substitution and stopping; modeling of positive self-evaluation)
Self-control therapy (Rehm)	Self-monitoring—gain control over and increase positive activities Self-evaluation—learn to set realistic goals; learn to make more accurate attributions regarding causes of successes and failures Self-reinforcement—learn to increase and maintain level of positive activities	Monitor mood Schedule pleasurable activities Set realistic goals, and break into operational subgoals. Schedule activities related to goals, and monitor progress. Teach patients to make correct self-attributions. Patients construct individualized self-reinforcement programs to increase and maintain level of positive activities.
Social learning therapy (Lewinsohn)	Initial 2-week diagnostic phase leading to behavioral diagnosis Treatment designed to increase activity level and enhance social skills	Home observation Daily monitoring of mood and activity Increase participation in pleasant events Decrease and manage aversive events Environmental interventions—environmental shifts, change consequences of certain behaviors Assertion training through modeling and rehearsal Set goals for increasing social activities Relaxation training Time management Cognitive techniques (include thought interruption, worrying time, disputing irrational thoughts, noticing accomplishments, positive self-rewarding thoughts)
Social skills training (Hersen and Bellack)	Skills training—patient is taught positive assertion, negative assertion, and conversational skills Social perception training—patient learns to attend to relevant context and cues of interpersonal interactions Practice—newly learned responses are carried out in the natural environment Self-evaluation and self-reinforcement—patient is trained to evaluate responses more positively and to provide self-reinforcement	Didactic instruction Modeling, guided practice of skills Role playing Homework assignments Monitoring and recording of homework performance by patient Patient evaluates role-played responses with letter grade; therapist corrects inappropriately low responses Therapist models positive self-statements

ship between increased pleasant activities and lower levels of depression.

Decrease or manage unpleasant events From the daily ratings, negative interactions or situations that trigger feelings of depression are identified. When possible, the patient learns to avoid or decrease unpleasant events. Patients are also taught to manage their reactions to negative events by learning to substitute more positive thoughts, to prepare for unpleasant events, and to prepare for failure.

Development of new self-reinforcement patterns The patients learn to reward themselves or to increase goal-related activities with material rewards or activities.

Enhance social skills Deficits in social skills and interaction patterns are addressed through assertiveness training, modeling, role playing with feedback and rehearsal or through providing graduated performance assignments to promote rewarding social interaction and decrease social avoidance, or they may be addressed by a combination of approaches. Group therapy sessions may be used to improve communication skills or to resolve specific interpersonal problems.

Relaxation training This training may aid in achieving other goals, such as increasing social interaction, reducing the aversiveness of unpleasant situations, or producing an affective state that is incompatible with depression. Patients are given instructions on relaxation of the major muscle groups, they are encouraged to practice relaxation twice a day, and they are instructed to keep a relaxation log.

Time management Training patients to plan ahead and make preparations necessary to participate in pleasant events, e.g. obtain a baby-sitter, is involved in time management. An effort is made to work out an appropriate balance between activities that they want to do and activities that they feel they have to do.

Cognitive skills training This training is generally geared toward decreasing negative thinking and increasing positive thinking. Patients are taught to monitor their thinking and to discriminate between positive and negative thoughts, necessary and unnecessary thoughts, and constructive and destructive thoughts. Specific techniques include thought-stopping, disputing of irrational thoughts, and correcting errors in attribution regarding causes of successes and failures.

EFFICACY Studies of various behavioral treatments have varied in terms of specific techniques tested, type of comparison groups, use of no active treatment control groups, and size and type of sample. Efficacy data have generally been positive for behavioral techniques in comparison with waiting list or nondirective groups.

COGNITIVE BEHAVIORAL THERAPY

THEORETICAL ROOTS AND CONCEPT OF DEPRESSION Cognitive behavioral (CB) therapy stems from four major theories: psychoanalysis, phenomenological philosophy, cognitive psychology, and behavioral psychology. Several threads emerge from these theories. Perhaps most salient is the recognition of the importance of the subjectiveness of conscious experience, i.e. the experience of reality, rather than objective reality. Another thread is the recognition of the emotional consequences of irrational beliefs.

Aaron Beck, the originator of CB theory, has developed a comprehensive and structured theory of depression. Depression consists of a cognitive triad; specific schemes; and cognitive errors, or faulty information processing (Table 18.6–5).

TABLE 18.6–5
Elements of Cognitive Theory

Element	*Definition*
Cognitive triad	Beliefs about oneself, the world, the future
Schemas	Ways of organizing and interpreting experience
Cognitive distortions	
Arbitrary inference	Drawing a specific conclusion without sufficient evidence
Specific abstraction	Picking out a single detail and ignoring other more important aspects of an experience
Overgeneralization	Forming conclusions on the basis of too little and too narrow experience
Magnification and minimization	Over- or undervaluing the significance of a particular event
Personalization	Tendency to self-reference to external events without basis
Absolutistic, dichotomous thinking	Tendency to place experience into all-or-none categories

The *cognitive triad* consists of negative cognitions regarding oneself, the world, and one's future. First is a negative self-percept involving seeing oneself as defective, inadequate, deprived, worthless, and undesirable. Second is a tendency to experience the world as a negative, demanding, and defeating place and to expect failure and punishment. Third is an expectation of continued hardship, suffering, deprivation, and failure.

Schemas are stable cognitive patterns through which one interprets experience. Schemas of depression are analogous to viewing the world through dark glasses. Depressogenic schemas may involve viewing experience as black or white without shades of gray, as categorical imperatives that allow no options, or as expectations that people are either all good or all bad.

Cognitive errors are systematic errors in thinking that lead to persistence of negative schemas in spite of contradictory evidence.

The cognitive theory of depression posits that cognitive dysfunctions are the core of depression and that affective and physical changes, and other associated features of depression, are consequences of the cognitive dysfunctions. For example, apathy and low energy are results of the individual's expectation of failure in all areas. Similarly, paralysis of will stems from the individual's pessimism and feelings of hopelessness.

GOAL The goal of CB therapy is to alleviate depression and to prevent its recurrence by helping the patient (1) to identify and test negative cognitions; (2) to develop alternative, more flexible schemas; and (3) to rehearse both new cognitive and new behavioral responses. The goal is also to change the way an individual thinks and subsequently to alleviate the depressive syndrome.

GENERAL CONSIDERATIONS CB therapy has been developed by Beck, and was described in operational detail by Beck, Kovacs, and Rush. It is a short-term, structured therapy that involves active collaboration between the patient and the therapist toward achieving the therapy goals. It is oriented toward current problems and their resolution. CB therapy is usually conducted on an individual basis, although group

techniques have been developed and tested. This therapy may be used in conjunction with drugs.

STRATEGIES AND TECHNIQUES As with other psychotherapies, therapist attributes are of fundamental importance to successful CB therapy. The therapists must be able to exude warmth, be able to understand the life experience of each patient, and be truly genuine and honest with themselves, as well as with the patients. Therapists must be able to relate skillfully to individual patients in their experiential world in a truly interactive way.

As a highly structured therapeutic approach, CB involves setting the agenda at the beginning of each session, assigning homework to be performed between sessions, and learning specific new skills. The active collaboration between the therapist and the patient provides a genuine sense of teamwork.

There are three basic components to CB therapy: didactic aspects, cognitive techniques, and behavioral techniques (Table 18.6–6).

Didactic aspects Didactic aspects include an explanation to the patient about the nature of the cognitive triad, schemas, and faulty logic. The therapist must explain to the patient that they will formulate hypotheses together and will test them over the course of the treatment. CB therapy involves a full explanation of the relationship between depression and thinking, affect, and behavior, as well as the rationale for all aspects of the treatment. This explanation is in contrast to more psychoanalytically oriented therapies, in which very little explanation is involved.

Cognitive techniques The cognitive approach includes four processes: (1) eliciting automatic thoughts, (2) testing automatic thoughts, (3) identifying maladaptive underlying assumptions; and (4) testing the validity of maladaptive assumptions.

Eliciting automatic thoughts Automatic thoughts are cognitions that intervene between external events and the individual's emotional reaction to the event. An example of an automatic thought is the belief that "everyone is going to laugh at me when they see how badly I bowl"—a thought that occurs to someone who has been asked to go bowling and responds negatively. Another example is a person's thought that "he doesn't like me," if someone passes that person in the hall without saying hello.

Testing automatic thoughts The therapist, acting as a teacher, helps the patient to test the validity of the automatic thought. The goal is to encourage patients to reject inaccurate or exaggerated automatic thoughts after careful examination.

Patients often blame themselves for things that go wrong that may well have been outside their control. The therapist reviews with the patient the entire situation and helps to "reattribute" the blame or cause of the unpleasant events more accurately. The case of a 51-year-old moderately depressed bank manager who complained of "ineffectiveness in my job" is detailed by Beck.

Patient: I can't tell you how much of a mess I've made of things. I've made another major error of judgment that should cost me my job.
Therapist: Tell me what the error in judgment was.
Patient: I approved a loan that fell through completely. I made a very poor decision.
Therapist: Can you recall the specifics about the decision?
Patient: Yes. I remember that it looked good on paper, good collateral, good credit rating, but I should have known there was going to be a problem.
Therapist: Did you have all of the pertinent information at the time of your decision?
Patient: Not at the time, but I sure found out 6 weeks later. I'm paid to make profitable decisions, not to give the bank's money away.
Therapist: I understand your position, but I would like to review the information that you had at the time your decision was required, not 6 weeks after the decision had been made.

In this example, when the patient and therapist carefully reviewed the situation, it became apparent that the patient's original decision was justified on the basis of those facts available at the time that the loan was made. The reasons for the default on the loan only came to light afterwards, and therefore, the blame could not be attributed to the patient for having made a bad decision.

Generating alternative explanations is another way of undermining inaccurate and distorted automatic thoughts.

A medical records librarian with a 6-year history of depression reported that the charge nurse in the coronary care unit was curt and said, "I hate medical records" when the librarian went to collect charts for the record review committee. The patient reported feelings of sadness, slight anger, and loneliness. Her automatic thought was, "She [the nurse] doesn't like me." The therapist helped the patient to elucidate other possible interpretations, such as the possibility that the charge nurse is generally unhappy, that she may be under pressure for reasons unrelated to the librarian, that hating medical records is not the same as hating the librarian, and that perhaps she actually hated paperwork.

Identifying maladaptive assumptions As the patient and therapist continue to identify automatic thoughts, patterns usually become apparent, representing rules or maladaptive general assumptions that guide the patient's life. Samples of such rules are, "In order to be happy, I must be perfect" or "If anyone doesn't like me, I'm not lovable." Such rules inevitably lead to disappointments and failure, and subsequently to depression.

Analyzing the validity of maladaptive assumptions Similar to the testing of the validity of automatic thoughts is the testing of the accuracy of maladaptive assumptions. One particularly effective technique for this test is for the therapist to ask the patient to defend the validity of the assumption.

Patient: I guess I believe that I should always work up to my potential.
Therapist: Why is that?
Patient: Otherwise I would be wasting time.
Therapist: What is the long-range goal in working up to your potential?
Patient: I've never really thought about that. I've just assumed that I should.
Therapist: Are there any positive things you give up by always having to work up to your potential?
Patient: I suppose it makes it hard to relax or take a vacation.

TABLE 18.6–6
Cognitive Behavioral Therapy

Components
1. Didactic Issues
Learning the therapy's rationale and strategy
2. Cognitive Techniques
Eliciting automatic thoughts
Testing automatic thoughts
Identifying maladaptive underlying assumptions
Analyzing validity of maladaptive assumptions
3. Behavioral techniques
Scheduling activities
Mastery and pleasure
Graded task assignment
Cognitive rehearsal
Self-reliance training
Role playing
Diversion techniques

Therapist: What about living up to your potential to enjoy yourself and relax? Is that important at all?
Patient: I've never really thought of it that way.
Therapist: Maybe we can work on giving yourself permission not to work up to your potential at all times.

In this example, the therapist helps the patient to recognize how maladaptive it is to strive to work up to one's potential at all times.

Behavioral techniques Behavioral techniques go hand in hand with cognitive techniques; behavioral techniques are used to test and change maladaptive or inaccurate cognitions. The over-all purpose of such techniques is to help the patients to understand the inaccuracy of their cognitive assumptions and to learn new strategies and ways of dealing with issues.

Among the behavioral techniques that are utilized in CB therapy are scheduling activities, mastery and pleasure, graded task assignments, cognitive rehearsal, self-reliance training, role playing, and diversion techniques.

Among the first things done in CB therapy is to schedule activities on an hour by hour basis. A record of these activities is kept and is reviewed with the therapist.

In addition to scheduling activities, patients are asked to rate the amount of mastery and pleasure of their activities. Patients are often surprised at how much more mastery and pleasure they get out of activities than they had otherwise believed.

In order to simplify the situation and allow for mini-accomplishments, tasks are often broken down into subtasks, as in graded task assignments, to demonstrate to patients that they can succeed.

Cognitive rehearsal involves getting the patient to imagine the various steps involved in meeting and mastering a challenge and to rehearse the various aspects of it.

Patients, especially inpatients, are encouraged to become more self-reliant, by such simple things as making their own beds, doing their own shopping, or preparing their own meals rather than relying on other people. This is *self-reliance training.*

Role playing is a particularly powerful and useful technique to elicit automatic thoughts and to learn new behaviors.

Diversion techniques are useful in helping patients to get through particularly difficult times and involve the implementation of physical activity, social contact, work, play, or visual imagery.

The techniques involved in CB are highly structured, goal-oriented, and involve active collaboration between the therapist and the patient. Emphasis is on identifying maladaptive, inaccurate cognitions in various forms, seeking alternative explanations, and learning new behaviors. The major principle involved in all of these techniques is that identifying and changing these cognitions and relevant behaviors will reverse the affective and drive disturbances, and other associated features of depression and, it is hoped, will help to prevent their recurrence.

EFFICACY Despite the large number of studies that have been reported using CB therapy, only a handful used adequate control groups and random assignment to treatment conditions. These studies all involved nonbipolar depressed patients or volunteers in the mild to moderate range, and treatment varied from 1 week to 3 months. Comparison groups included tricyclic antidepressants, behavioral therapy, and wait list. Over-all, CB tended to be more effective in reducing depressive symptoms and had a lower attrition rate than other treatments.

FAMILY AND MARITAL THERAPY

THEORETICAL ROOTS AND CONCEPT OF DEPRESSION Unlike the specific psychotherapeutic approaches discussed previously, family therapy comprises a group of therapies with diverse theoretical roots and therapeutic techniques. Despite their many differences, however, all family therapies share a focus on the family as a system, an emphasis on relationships rather than on individuals, and the view that positive changes in the functioning of the system will beneficially affect individual family members. This approach therefore differs almost diametrically from IPT, which approaches depression much more as a "disease" of the individual.

Approaches to the treatment of dysfunctional families range from those based on psychoanalytic theory, in which the therapist may help the family members analyze their unconscious needs and wishes that adversely impact family functioning, to strategic family therapy, which may focus on solutions to specific problems within the context of the existing family hierarchy. In addition, there is a broad middle ground of system-oriented family therapies in which the complex interaction matrix of the family is the focus of treatment. Finally, the various cognitive and behavioral techniques described in earlier sections have been applied within family and couples contexts.

Given such a diversity of theoretical orientations, it is perhaps not surprising that, within family therapy, there has emerged no unitary view of depression. Furthermore, family therapy has not evolved with the treatment of depression as a primary focus, nor have techniques been developed for specific use in depression. This is not to suggest that family therapy techniques cannot be applied to marital and family units with a depressed member, but rather that treatment of such cases would proceed according to the format of family therapy in general.

GOALS The over-all goals of family therapy are to facilitate improved psychological functioning and increase satisfaction of family and marital units and their individual members. In order to achieve these goals, family therapists generally attempt to clarify and alter individual expectations and dysfunctional interaction patterns. These goals remain the same for families in which there is a depressed member.

GENERAL CONSIDERATIONS Family therapy is not generally viewed as a primary therapy for the treatment of depression, but its use is indicated in cases where (1) an individual's depression appears to be seriously jeopardizing that person's marriage or family functioning or both, or (2) an individual's depression appears to be promoted and maintained by marital or family interaction patterns or both. Family therapy examines the role of the depressed member in the over-all psychological well-being of the whole family; it also examines the role of the entire family in the maintenance of the depression. This approach has especial salience when the depressed individual is the mother of young children. In general, however, diagnosis of family dynamics should be approached cautiously when one of the members is acutely depressed. Family interaction patterns may have been substantially disrupted by the depression.

STRATEGIES AND TECHNIQUES Depending on the theoretical orientation of the therapist, the goals of family therapy are achieved through a variety of techniques that range from interpretation to direct alteration of interaction patterns.

No techniques have been developed within the various family therapies specifically for depression. Instead, when

treating a family or couple with a depressed member, the general techniques of family therapy would be applied.

EFFICACY No literature is available on the comparative efficacy of family and marital therapies in the treatment of depression. In an investigation of the effects of antidepressant therapy versus marital therapy, alone and combined, in the treatment of depressed outpatients, a combined treatment approach was associated with best outcome.

DISCUSSION

Several other factors are relevant to the choice of, and success of, a particular psychotherapeutic treatment for depression. These include diagnosis, chronicity, mode of therapy, combination psychotherapy and medication, and other influencing variables.

DIAGNOSIS In general, these psychotherapeutic approaches were developed for, and are recommended primarily for, nonbipolar depressions in the mild to moderate range that meet DSM-III criteria for major depressive disorder or dysthymia in patients of moderate intelligence or above. Some controversy exists over which nonbipolar depressions should first be treated with medication, but certainly, patients who are very suicidal or present with hallucinations or delusions or both are not considered to be good candidates for these approaches. In general, patients meeting criteria for melancholia first ought to be given a trial of medications or be given medications in combination with psychotherapy.

Since the discovery of the efficacy of lithium in the treatment of bipolar disorder, little if any attempt has been made to develop specific techniques for patients with bipolar depressive disorder, beyond marital or various supportive techniques. This is unfortunate, because bipolar disorder is especially destructive for the individuals and their families and psychotherapeutic techniques may be very useful.

CHRONICITY Recognition of the pernicious problem of chronicity in depression is growing. Up to 20 percent of individuals with an episode of depression will become chronic, and an additional 30 to 40 percent will have episodic recurrences. Furthermore, many patients develop an episode of major depression after several years of mild chronic, characterological depression. The outcome for these patients is much worse than for other patients. The role that psychotherapy may play in the treatment of such patients is, unfortunately, largely unknown.

MODE OF THERAPY Individual psychotherapy has been the standard mode of treatment for the specific psychotherapies described in this chapter. Some of these psychotherapies, however, would seem to be particularly well suited to therapeutic modes other than individual psychotherapy. For example, interpersonal therapy using a family mode would seem to be a logical choice for a marital dispute. Testing cognitive distortions about one's social presence may be very easy to do in group therapy. Group therapy allows for development of a number of transference relationships, rather than a single one between the therapist and the patient. Development of social skills is made easier in a group situation.

COMBINATION PSYCHOTHERAPY AND MEDICATION Depression is a complex group of disorders that involve many body systems. Medications may be advisable in certain depressions, whereas psychotherapeutic approaches are preferred in others. In many cases, a combination of drugs and psychotherapy may be best. There is some evidence to support the notion that drugs tend to affect the specific somatic and vegetative symptoms of depression, whereas psychotherapies affect interpersonal and cognitive aspects. Therefore, a comprehensive approach would involve both modalities complementing one another.

OTHER INFLUENCING VARIABLES A number of other issues may affect outcome of a particular treatment and, therefore, affect selection of the treatment. These issues include premorbid personality, concurrent personality disorders, and expectations of therapy.

Many patients with depression have been described as having premorbid personalities characterized by increased interpersonal dependency, whereas others are considered more obsessional. These personality features could well affect vulnerability to subsequent depressive episodes and may well affect treatment considerations. Patients with excessive dependency may not be good candidates for short-term psychoanalytic therapies because dependency on the therapist may become too great and termination too disruptive. Obsessional patients, however, may do much better when transference issues are actively confronted.

The importance of concurrent personality disorders is only recently beginning to be appreciated. Treatment of patients with borderline personality disorder would certainly be different from that of someone with paranoid personality disorder and, again, may be very different from the treatment of someone with avoidant personality disorder. Patients with avoidant personality disorder may do much better in behavior therapy, where social skills are increased in a safe environment; however, the social approach may be less effective for someone with paranoid personality disorder. A cognitive approach may be much better for these latter patients.

The expectations of the patient should also be considered. Some patients consider depression to be a psychological disorder that ought to be amenable to psychotherapeutic approaches, and they are resistant to the use of medication. Other patients have exactly the opposite expectations; they may consider their depression to be a biochemical disturbance that will require medication if it is to be corrected, and not psychotherapy. A good therapist may be able to modify such expectations when necessary, but a positive attitude about treatment on the part of the patient may be very important to successful outcome.

In general, the therapist should be advised to be cautious in making attributions about premorbid personality problems during the depressed phase. Many interpersonal and cognitive styles may appear very different to the patient and the therapist following alleviation of the acute phase of the disorder.

The theoretical rationale and basic strategies of each of the specific psychotherapies that have been described are distinct from one another; yet, in spite of these distinctions, considerable overlap exists among the approaches. All recommend an empathic, understanding approach by the therapist who enters into a collaboration with the patient, rather than simply delivering a treatment. Most approaches include an education regarding the nature of depression and the techniques involved in the treatment. Interpersonal issues are central to all therapies, and most of them encourage behavioral change and judicious management of current crises.

What accounts for change is not clear at this time. Probably the answer will be complex; certain psychotherapeutic strategies will yield certain kinds of change, e.g. CB for changes in maladaptive assumptions, whereas general characteristics may account for other changes, e.g. a warm, accepting therapist manner may be responsible for a general uplifting in self-esteem. Elucidation of these active ingredients for affective,

cognitive, and behavioral change is the next great task for psychotherapy research.

SUGGESTED CROSS REFERENCES

Specific methods of psychotherapy are discussed in various other sections: psychoanalysis and psychoanalytic psychotherapy in Section 29.1, behavior therapy in 29.2, group therapy in 29.5, family therapy in 29.6, and marital therapy in Section 29.9. Short-term dynamic psychotherapy is covered in Section 29.11, and occupational therapy and other therapeutic activities are covered in Section 31.3. Psychoanalytic therapy is discussed in great detail in Chapter 8. For a further discussion on affective disorders see Chapter 18.

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18.7 AFFECTIVE DISORDERS: PHARMACOTHERAPY

ANASTASIOS GEORGOTAS, M.D.

INTRODUCTION

HISTORY Homer elegantly describes what may be the first recorded use of a drug for the relief of depression. In the *Odyssey*, he refers to *nepenthes* (probably an opium derivative), which Helen of Troy gave to Telemachus and his companion to relieve their grief: "Presently she cast a drug into the wine ... to bring forgetfullness of every sorrow ...." Around the same time, on the Greek island of Lefkas, temple priests were throwing depressed patients into the sea from a cliff 200 m high. (Ironically, it was the same cliff from which Sapfo committed suicide.) Waiting in the boats below, the priests retrieved the patients from the sea. According to accounts written at the time, many of these victims recovered after receiving what may conceivably be called the first shock treatment for depression.

It is fascinating that these historical counterparts of today's biological treatments occurred well before Hippocrates' first clinical description of melancholia, perceived as an abnormal state of depression caused by circulating black bile, with its inherent biological intimations.

The origin of the pharmacotherapy of mania dates back to the 2nd century A.D. During this period, the Greek physician Seranus Ephesios, in his writings on the treatment of mania, advocated "natural waters such as alkaline spring," many of which contained lithium. The burst of initial progress was followed by a relatively dormant period, which was to last for over 3,000 years.

Around 1818 Arfwedson discovered lithium, and in 1891 iminodibenzyl (the parent compound of tricyclic antidepressants) was synthesized by Thiele and Holzinger. Cade accidently discovered lithium's antimanic efficacy in 1949, while a few years later a serendipitous recognition of iminodibenzyl's antidepressant efficacy was made by Kuhn. Subsequent clinical trials confirmed the antimanic and antidepressant properties of both these drugs, which were introduced in the United States shortly thereafter, revolutionizing the treatment of affective disorders.

CLINICAL CONSIDERATIONS

DIAGNOSTIC ISSUES An important principle in rational therapeutics is to *know* what is being treated, i.e. to have a thorough knowledge (Greek; *διάγνωσις*-diagnosis) of the underlying disease process. Unfortunately, in the treatment of affective disorders, where many deviations of normal mood are indiscriminantly treated with an array of potentially dangerous drugs, this basic axiom is sometimes forgotten. This tendency is reminiscent of the time when every anemia was treated with iron. Prominent sources of this confusion are (1) lack of conceptual clarity regarding the syndromes of depression and mania, i.e. the blurring of their boundaries where they intersect with either normal mood states or with other psychiatric conditions; (2) problems in classification; and (3) incomplete pharmacological knowledge.

One of the primary reasons for the ambiguity of the concept of depression and mania is the difficulty in distinguishing between these syndromes and normal changes in degree and quality of mood, such as sadness, grief, and demoralization, on the one hand, and euphoria, anger, and elation, on the other hand. Niobe's transformation to an eternally lacrimating stone, following the not so god-like brutal killing of her 14 children by Apollo and Artemis, would, in her day, have hardly been conceived of as the first documented description of *melancholia anaesthetica* or stuporous depression. By today's confusing standards, however, it might well be misdiagnosed as catatonic schizophrenia. As compared to depression, mania is more easily recognized as distinct from normal. Homer had no difficulty in diagnosing Ajax as maniacal, although he almost missed the suicidal depressive phase of his rapidly cycling behavior. The same trend is found in Shakespeare's legendary description of Hamlet's manic-depressive state. Throughout history, mania has been equated with madness, whereas in most societies, depression has been considered to be a normal mood variant. Indeed, melancholic traits have frequently suggested a certain charismatic sensitivity, refined nature, and cultural proclivity and have long been appreciated, or even idealized, by poets (Homer, Sappho, David) and philosophers (Plato, Aristotle, Schopenhauer) alike. The tendency to idealize depression has continued, uninterrupted, through the centuries, reaching its peak in Europe at the beginning of the 20th century with the fashionable mass suicides of the Schopenhauer era.

Despite the many commendable attempts to characterize the manic and depressive syndromes in terms of clinical variables, including some recent criteria, such as symptom cluster, duration, pervasiveness, and interference with func-

tion, the distinction between these syndromes and normalcy remains problematic.

The distinction between affective disorders and schizophrenia is also unclear. This lack of clarity is exemplified by the misnomer "schizoaffective schizophrenia," which refers to a mixed clinical state with concurrent schizophrenic and affective symptomatology, of questionable meaning and nosological significance. Attempts to define this concept longitudinally or cross-sectionally have not been very successful, and the meaning of schizoaffective schizophrenia remains unclear. Similar problems are encountered with the mixed depressive-anxiety states, despite extensive efforts to separate the two states in terms of premorbid personality traits (high neuroticism scores in anxiety states), and current symptomatology (more anxiety and panic attacks in anxiety states, more vegetative signs in depressive states).

Differential diagnosis becomes even more problematic in the elderly, where presenting symptoms are frequently complicated by superimposed cognitive impairment. Determining the real importance of organic versus functional disease and differentiating early stages of dementia from depressive pseudodementia (functional depression) may be very difficult. Common presenting features include apathy, disinterest, and memory defects in an elderly patient who seems "perplexed." These signs and symptoms may be indicative of depression, organic brain disease, or both. Complaints of poor memory may accompany functional depression and may disappear when the depression is treated. A very early organic brain disease with a gradual decline in cognitive functioning frequently leads to a reactive depression, which in turn may lead to further increase in cognitive impairment.

It has been pointed out that the symptoms of depression precede those of cognitive loss in cases of depressive pseudodementia, whereas the reverse is true in cases of dementia. At times, "near miss" answers to questions testing cognitive function suggest organicity, whereas "don't know" answers are more common in depressive pseudodementia. In addition, depressed patients with pseudodementia have an abrupt onset and often communicate a sense of distress, whereas in patients with early dementia there is a progressive deterioration of cognitive functioning, and the emotions are usually shallow. Also these patients do poorly on some tests of memory and intelligence, but unexpectedly well on others. Quite often in such cases there is a personal or family history of depression. Patients with dementia generally do not report feeling sad or depressed, and they have a tendency to confabulate. In addition, patients with functional depression tend to complain more frequently about confusion, memory difficulties, and fluctuating levels of disorientation. Patients with early stages of dementia are much less concerned about their cognitive impairment, usually noticeable to relatives and close friends, and have a tendency to deteriorate steadily.

At the present time, there seems to be an effort to develop and utilize more objective measures of psychiatric symptoms and to correlate these measures with neurophysiological, neurochemical, and neuroanatomical findings. As investigators move in the direction of this process of objective and converging operations, they may be able to move away from the descriptive past and into a scientific future.

Classification within affective disorders is even more confusing and controversial. Some of the most common nosological systems, such as unipolar versus bipolar, psychotic versus neurotic, endogenous versus nonendogenous, and primary versus secondary, do not correspond to etiologically well-defined categories. These dichotic systems tend to emphasize different aspects of the same disorder, such as course, intensity, chronicity, symptoms, or precipitating events. It is not clear how these systems are related to each other. At times, they are overlapping, although not necessarily synonymous, i.e. characterological, neurotic, reactive, hysteroid, psychological existential depression. There is, however, considerable consensus among clinicians and researchers in the field concerning the validity of the unipolar-bipolar distinction, which is based on genetic, biochemical, clinical, and pharmacological findings. The endogenous or endogenomorphic subtype of the endogenous-nonendogenous dichotomy is also useful, and it is well defined phenomenologically in terms of characteristic symptom profile, positive response to biological treatments (drugs or electroconvulsive therapy), and favorable long-term outcome. This symptom profile includes pervasive loss of interest and pleasure (*anhedonia*), qualitative mood changes, lack of reactivity to external stimuli (*autonomy*), diurnal mood variation (worse in the A.M.), middle and late insomnia, psychomotor disturbances, anorexia, and weight loss. This subtype is almost identical with the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) subdivision of melancholia or with the vital depressions noted by some European investigators.

The endogenomorphic subtype has an increased genetic loading of depression and has been correlated with levels of amine metabolites (MHPG, 5-HIAA); decreased rapid eye movement (REM) latency; neuroendocrinological parameters, such as blunted thyroid-stimulating-hormone (TSH) response to thyrotropin-releasing-hormone (TRH), hypercortisolemia, escape from dexamethasone suppression; and variation in response to certain pharmacological challenges, such as growth hormone response to amphetamine infusion, as well as increased cholinergic sensitivity following injection of cholinergic agonists.

In clinical practice, however, the patients encountered may either have a subclinical form of one subtype or have mixed features. The real difficulty in achieving agreement between clinicians is in defining an acceptable boundary, one that would satisfy the clinician's need for adequate flexibility and diagnostic sensitivity of such patients, rather than classify them according to a dichotomous category. The DSM-III is more sensitive to the clinician's needs by allowing some overlap among the different subtypes of the Affective Disorders class. DSM-III has adopted the term Affective Disorders, under which heading all the different subtypes of depression are subsumed. Affective Disorders are divided into three main groups: major affective disorders (episodic), other specific affective disorders (chronic cyclothymias and dysthymias), and atypical affective disorders. The major affective disorders are further divided into major depressive episode (similar to unipolar depression) and bipolar disorder. Melancholia (comparable to endogenous subtype) is a subtype of the major depressive episode.

PHYSICIAN'S SELF-EVALUATION The ability to structure and execute an effective treatment plan, suited to each individual patient, requires that clinicians evaluate their own expertise in relation to recent progress in the understanding and treatment of depression derived from both biological and behavioral research. The physician's armamentarium for the treatment of this illness includes both biological and psychotherapeutic procedures. Recent clinical studies indicate that a combination of psychotherapy and biological treatment provides maximum benefit to patients, with no negative interactions and, possibly, an additive effect. Aside from some special psychotherapeutic techniques—such as psychoanalysis and cognitive, behavioral, group, and family therapy—indi-

vidual psychotherapy based on common sense, sincere concern, and essential psychodynamic and cognitive principles can be very helpful in conjunction with rational pharmacotherapy. Psychiatrists are not merely therapists or psychopharmacologists, in the same way that cardiologists are not cardiopharmacologists. A well-trained psychiatrist should be able to provide both optimal psychotherapy and pharmacotherapy.

SUPPORT SYSTEM Family and social support systems are extremely important and should always be considered before any treatment plans are made. Clinical research supports the familiar idea that availability of significant others can be a major determinant in the successful management of depressed patients.

DEPRESSION

CHOICE OF TREATMENT **Selection of patients** A clinician who is thoroughly familiar with the most up-to-date diagnostic procedures will best be able to evaluate the patient's condition without relying on personal biases, sociocultural attitudes, and preconceived notions that are commonly covered under the rubric "experience." The utilization of such procedures, coupled with a complete medical-neurological examination, should enable the clinician to distinguish depression from other psychiatric (schizophrenia, alcoholism) and medical illnesses. Appropriate evaluation should also assist in identifying the particular depressive subtype and should facilitate a sound treatment plan.

The social acceptability of depression, the availability of effective antidepressants, and the resulting optimism concerning the prognosis of depression have contributed to the expansion of the Affective Disorders class. Nonetheless, a recent concurrent trend toward the indiscriminant use of antidepressants has had adverse consequences. This trend has resulted in increased incidence of side effects and has fostered poor predictive validity, thereby impairing the clinician's credibility.

It is important to remember that for many depressed patients, even if they meet the DSM-III criteria for certain subtypes of Affective Disorders, pharmacotherapy has little to offer, other than satisfying the magical expectations of both the therapist and the patient. These mutual expectations probably account for the high success rates resulting from indiscriminate use of various antidepressants. These rates are not very different from placebo response rates, both being about 50 to 60 percent.

Response predictors Some of the best clinical predictors of positive response to tricyclic antidepressants (TCA's) or electroconvulsive therapy (ECT) are endogenomorphic symptoms currently included under the DSM-III subtype, melancholia. Poor outcome has been associated with high neuroticism; depression associated with realistic life events, such as incapacitating medical illness or significant loss; as well as with bipolarity, severe agitation, anxiety, and cognitive disorganization. Recent studies by the author indicate that endogenomorphic or melancholic symptomatology—mainly anhedonia, autonomy, feelings of emptiness, and distinct quality of depressed mood—a family history of depression, as well as episodicity with normal interval functioning, have a high diagnostic validity, have been associated with almost 80 percent escape from dexamethasone suppression, and exceed 90 percent response rate to tricyclic antidepressants.

Recently, favorable outcome to pharmacotherapy has also been suggested for a subgroup currently included under the DSM-III term "dysthymic disorder" (or depressive neurosis). These chronic depressive patients seem to manifest a subclinical form of major depression, as evidenced by shortened REM latencies, abnormal dexamethasone suppression test (DST), and positive family history of depression. Phenomenologically, these patients exhibit some attenuated endogenomorphic features, such as anhedonia, guilt, and hypersomnia, i.e. gloomy, passive, self-critical.

The presence of delusions has been the source of controversy concerning the relationship between delusions and severity. Symptomatically, delusional depressive patients appear to have significantly more psychomotor retardation or agitation, guilt feelings, ruminating self-referential thinking, and affect-congruent delusions and hallucinations. They respond poorly to antidepressants, and they should be treated by combining TCA's with neuroleptics, lithium (Lithonate, Rowell), or ECT.

Among the biological predictors, response to the dexamethasone suppression test (DST) and some of the sleep electroencephalogram (EEG) parameters appear to be the most promising. Thus, it has been reported that depressed patients with less than 80 percent sleep efficiency (REM latency between 21 and 70 min) respond favorably to TCA's, whereas REM latency of less than 20 min is associated with poor response.

Abnormal DST results (cortisol levels above 5 μg/dl) are strongly associated with positive response to TCA's. Studies by the author indicate that more than 90 percent of endogenomorphic nonsuppressors had a complete recovery following treatment with TCA's. Because of its simplicity, DST, if properly performed—after exclusion of medical and metabolic conditions or interfering drugs and in clinical settings where the prevalence of melancholia is around 35 percent—appears to be a powerful predictor of treatment response in the hands of a skillful clinician.

Positive clinical response to acute amphetamine challenge may also predict favorable response to TCA treatment; however, the value of this test as a routine part of treatment needs further investigation.

Severity The choice of treatment is based not only on detailed diagnostic evaluation but also on the severity of depression. Mildly depressed patients often do well with psychotherapy alone. If considered at all, drug use should be limited and supplementary to psychotherapy. For moderately depressed patients, optimal treatment consists of a combination of psychotherapy and antidepressants. TCA's are usually the initial choice, although monoamine oxidase inhibitors (MAOI's) may be considered under certain circumstances. For bipolar depressed patients, the addition of lithium may potentiate the antidepressant effect and will prevent switches into mania. For severely depressed patients, antidepressants supplemented by supportive individual or milieu therapy is the treatment of choice. ECT is usually the treatment of choice when delusions are present, when there is a high risk for suicide or an increased vulnerability to drug toxicity (elderly, medical conditions), or even when fast recovery is required because of crucial personal or professional obligations. Recovery from ECT is followed by treatment with TCA's.

SUICIDAL RISK A careful estimate of suicidal risk—30 times greater than that of the general population—is an integral part of any thorough assessment of depressed patients. About 10 to 15 percent of depressed patients will commit

suicide, and these rates are almost identical in bipolar patients. The risk for suicide is greater early in the course of the illness and is higher for men. The poor predictability of this condition, together with insufficient training of the clinician (at times coupled with the clinician's biases) makes this step very difficult. Clinical features usually associated with increased suicidal risk are (1) personal history of suicidal attempts, (2) intense suicidal drive, (3) history of acting out as the main expression of anxiety, (4) lack of family or social support, (5) significant losses, (6) hostility, (7) intense guilt, (8) anhedonia, (9) bipolar patients switching rapidly from manic to depressed phase, and (10) well-established refractoriness to previous treatments. Questions about suicide should always be asked, but in a very tactful manner that avoids stark confrontations and after a positive and trusting relationship with the patient has been established. Bald denials, especially when accompanied by inappropriate affect (smile), intense feelings of hopelessness, helplessness, and worthlessness, negative feelings, alienation from the environment, and dreadful feelings of emptiness, offer clues to increased risk and strongly suggest close supervision, preferably in an inpatient setting.

EFFECTIVE TREATMENTS Tricyclic antidepressants

CHOICE OF DRUGS TCA's are the treatment of choice for most endogenomorphic depressed patients. In studies that compared the various TCA's, no differences in clinical effectiveness were found; nevertheless, for some unknown reason, certain patients may do better on a particular TCA. The TCA's do, however, differ considerably from one another with regard to potential sedative, anticholinergic, and cardiovascular side effects. Amitriptyline (Elavil, Parke Davis) and doxepin (Sinequan, Roerig) have the strongest sedative and anticholinergic properties, whereas protriptyline (Vivactil, Merck Sharp & Dohme) has the least sedative, nortriptyline (Pamelor, Sandoz) has the least hypotensive, and desipramine (Norpramin, Merrel Dow) has the least anticholinergic properties. A rational choice of antidepressant may depend on the patient's drug history and tolerance of the drug's side effects.

PHARMACOKINETICS AND PLASMA LEVEL MONITORING TCA's are easily absorbed by the gastrointestinal tract and are metabolized mainly in the liver (hepatic microsomal enzymes). The first breakdown products of amitriptyline (AMI) and imipramine (IMI) (Tofranil, Geigy), nortriptyline (NT) and desipramine (DMI), respectively, are active. Evidence has accumulated that suggests that the hydroxy metabolites of certain TCA's are also active and potentially related to the cardiovascular effects of these drugs; TCA's are highly lipophilic and demonstrate a high degree, around 90 percent, of protein binding. The amount of drug available to the target tissue is only that which is unbound to plasma proteins. It is this portion that is pharmacologically active.

The tissue concentration of TCA's can be inferred more accurately from plasma concentrations than from oral usage. It is well known that different persons, at the same oral dose of TCA's, can show a 10- to 20-fold variation in plasma levels. This variation appears to be related to genetically determined differences in pharmacokinetics. Some of the important factors responsible for this interindividual variability are metabolism (the most important), absorption, and total volume of distribution. Metabolic rate and, consequently, steady-state (SS) levels are affected by several factors; thus smoking, sedative-hypnotics, and alcohol may lower the SS levels, whereas neuroleptics and amphetamine can increase them.

TCA's have an extensive elimination half-life enabling single daily dose administration. During initiation of treatment, or when the dosage is altered, it takes about 1 week (4 to 5 half-lives) to achieve SS levels. Therefore, blood for plasma concentration should be obtained 12 hours after the last dose and at least 1 week subsequent to the last dosage readjustment.

There is a relationship between plasma concentrations of certain TCA's (IMI, NT, DMI) and therapeutic outcome in endogenomorphic depression. The shape of this relationship for NT is an inverted U (curvilinear); that is, low and high plasma concentrations are associated with poor outcome, whereas moderate levels within the "therapeutic range" of approximately 60 to 160 ng/ml are associated with good outcome. For IMI, a linear relationship has been reported in nondelusional endogenomorphic patients, with a maximal effect most often occurring around 200 ng/ml (± 20) of IMI in addition to its desmethylated metabolite DMI. A recent study of DMI has suggested a linear relationship with a threshold concentration of 125 ng/ml, above which amount this drug is likely to be effective. For AMI, it is less clear whether the relationship is linear or curvilinear, although most studies have indicated some significant relationship between AMI plasma levels and clinical response. Limited information is available with regard to the other TCA's.

Given the present state-of-the-art, routine monitoring of TCA's is not indicated. Such monitoring should be reserved, however, for patients who do not respond to a usual clinical titration of the dosage after 2 to 4 weeks of treatment, for patients at risk (elderly, heart problems), for patients who develop adverse reactions at normal therapeutic dosages (slow metabolizers), and for patients suspected of noncompliance. The majority of depressed patients can be easily maintained with careful clinical titration alone or, at best, combined with a single plasma level monitoring, preferably accomplished 2 weeks after the maximum daily dose has been stabilized. Because very few laboratories can provide reliable TCA determinations, a laboratory with an established record in this area should be used. Even the most reliable reports should always be considered within the clinical context of the particular patient, and they should never outweigh clinical judgment.

BEGINNING TREATMENT Suggested therapeutic dosage ranges for available TCA's are provided in Table 18.7–1. In routine clinical practice, it is preferable to start with a test dose (25 mg IMI or AMI), and if well tolerated, to gradually increase over the first week to approximately two-thirds—that is, 200 mg for IMI, DMI, and AMI; 75 mg for NT—of the maximum recommended dosage. If clinical improvement begins (usually reported at the second weekly visit), the dosage remains unchanged until the third week. If, by this time, the patient has not completely recovered, the dosage is increased to the upper recommended limit—300 mg for IMI, DMI, and AMI; 100 to 125 mg of NT. When signs of clinical recovery do not appear by the end of the second week, the dosage is increased to the upper limit at this visit. In selected cases—patients at risk, or when rapid recovery is strongly indicated—a plasma level monitoring, prior to dosage increase, can provide very useful information regarding actual levels of IMI, DMI, and NT. During this period of dosage adjustment, the patient should be closely observed.

If, as usually happens with about 15 to 20 percent of patients, the patient's condition remains unchanged after at least 2 weeks at the maximum tolerated dose, plasma level monitoring is indicated. If it is within the therapeutic range—around 200 ng/ml for IMI or DMI and between 60 to 160 ng/ml for NT—another TCA with a different effect on reuptake should be tried. Alternative choices include switching to a second generation antidepressant, such as maprotiline (Ludiomil, CIBA), trazodone (Desyrel, Mead Johnson), or amoxapine (Asendin, Lederle) or to an MAOI or ECT. In cases of delusional depressions, these measures, with the exception of

TABLE 18.7–1
Approximate Daily Dosage Ranges of Currently Available Antidepressants

Tricyclic Antidepressants			*MAOI's*	
Drug	*Therapeutic Range (mg)*	*Maintenance (mg)*	*Drug*	*Dosage Range (mg)*
Imipramine (Tofranil)	150–300	75–150	Isocarboxazid (Marplan)	10–30
Amitriptyline (Elavil)	150–300	75–150	Phenelzine (Nardil)	30–75
Desipramine (Norpramin)	150–300	75–150	Tranylcypromine (Parnate)	10–30
Nortriptyline (Aventyl)	50–125	25–75		
Doxepin (Sinequan)	200–400	30–200	*Second Generation Antidepressants*	
Protriptyline (Vivactil)	30–60	10–30	Amoxapine (Asendin)	200–600
Trimipramine (Surmontil)	150–300	75–150	Maprotiline (Ludiomil)	75–300
			Trazodone (Desyrel)	150–600

ECT, will not usually suffice, and a combination with neuroleptics or lithium may prove effective. If this combination fails, ECT is the treatment of choice.

If facilities for plasma level determinations are readily available, an alternate and more sophisticated selection of dosage regimen is suggested (at present, only for NT, IMI, or DMI), utilizing a dose prediction test. A single oral test dose of 50 mg NT, IMI, or DMI is administered. Based on the antidepressant concentration obtained 24 hours later and on appropriate normograms, the physician can determine, with increased accuracy, the daily dose necessary to achieve SS levels within the therapeutic range. This dosage can be safely administered within the first week and can remain unchanged for at least 3 weeks. At the end of the third week, if no signs of clinical recovery appear, a second plasma level should be obtained; and if it is not within the therapeutic range, an appropriate dosage readjustment should be implemented. If the plasma level is within the therapeutic range, alternative treatments should be considered.

Monoamine oxidase inhibitors The MAOI's have recently been revived. Their earlier use was curtailed by reports of hepatic toxicity and hypertensive crisis; however, subsequent well-controlled studies have found them to be at least as safe and effective as TCA's in a large number of depressed patients. These studies also suggested that 85 percent of platelet monoamine oxidase (MAO) needs to be inhibited before clinical improvement occurs. For phenelzine (Nardil, Parke Davis), a dosage of about 1 mg/kg/day generally achieves near 85 percent inhibition. Similar findings also have been reported in geriatric depressed patients where platelet MAO inhibition greater than 80 percent seems to optimize clinical response to phenelzine.

Earlier claims that these drugs are only effective for atypical, neurotic, or hysteroid depressive patients have not been substantiated in more recent controlled studies. MAOI's may be effective in a wider variety of affective disorders, including endogenous depression, especially if they are associated with high anxiety scores.

When starting treatment with MAOI's, it is advisable to prescribe one tablet for the first 1 to 2 days and, within the first 2 weeks, gradually increase the dose to 3 to 4 tablets daily (around 0.8 to 1 mg/kg). Patients should be given written instructions regarding the avoidance of particular drugs (sympathomimetics) and tyramine-containing foods. Hypertensive crises, precipitated by ingestion of tyramine, are usually heralded by an atypical headache and constitute a medical emergency. In such cases, aggressive intervention to lower blood pressure (BP) utilizing phentolamine (Regitine, CIBA), 2.5 to 5 mg intravenously (IV), is lifesaving, followed with 0.25 to 0.5 mg IV every 4 to 6 hours to maintain BP control. Oral or IV chlorpromazine (Thorazine, Smith Kline & French) is also helpful. It is hoped that the second generation selective MAOI's with no tyramine effect will make treatment with these agents much safer.

Dose ranges for the three MAOI's are included in Table 18.7–1. In general, therapeutic effect takes place in 2 weeks, which is roughly the same time period necessary for response to TCA's.

A thorough understanding of the potential interactions of these drugs, as well as proper selection and education of patients regarding potential toxicity, are essential requirements for optimal treatment.

Second generation antidepressants These newer compounds, such as the tetracyclics (maprotiline, mianserin), trazodone, zimelidine, and nomifensine, although of similar therapeutic potency as the TCA's, have been reported to have fewer adverse effects, particularly anticholinergic.

At present, four second generation antidepressants have been marketed in the United States: amoxapine; maprotiline; trimipramine (Surmontil, Ives); and trazodone. The efficacy of these compounds has been established through extensive clinical trials and has been found to be equal to that of the TCA's. These antidepressants may also be effective across a wider spectrum of depressive subtypes. This fact is particularly true for trazodone and is slightly less so for amoxapine and maprotiline. In addition, limited data suggested that they may be faster acting than the first generation antidepressants, although both these claims should be further investigated.

At the present time, these compounds should hardly be routinely considered as a first choice drug for depressive illness. Nonetheless, because of their different pharmacological profile, they should be utilized as alternative treatments in certain patients refractory to, or intolerant of, standard antidepressants.

COMPLIANCE Noncompliance is a frequent (about 20 percent) cause of treatment failure. Compliance can be reinforced by a strong therapeutic alliance, a warm and rigorous education of patients—in terms of diagnosis, proper selection of the appropriate TCA, prognosis, pharmacotherapy, and side effects—and by individual measures to improve concurrent physical and socioeconomic instabilities. At times, a single dose schedule can substantially improve compliance, provided concomitant side effects, such as orthostatic hypotension, are not problematic.

REFRACTORY DEPRESSIONS Treatment failure has been associated with a number of diverse variables. Correlations have been found between poor response and high neuroticism score, severe anxiety and agitation, presence of delusions, bipolarity, inadequate dosage, poor compliance, low TCA plasma levels, inadequate degree of MAO inhibition, and insufficient treatment duration. An acknowledgment of the role of these factors should temper the clinicians' and patients' expectation of magical—that is, quick and dramatic—recovery. As more information concerning the characteristics associated with inadequate response becomes available, it will

guide treatment and, it is hoped, will decrease the percentage of refractory patients (currently 20 to 30 percent) to less than 10 percent. For well-documented cases of treatment failures, the clinician has the choice of switching to a standard antidepressant with a different pharmacological profile. ECT is another choice, but its administration depends on the circumstances, such as severity or suicidal risk. ECT remains the most effective treatment for refractory depressives. In instances where all treatment attempts fail, or when the patient adamantly refuses ECT, drug combinations should be carefully considered. TCA's may be combined with MAOI's, lithium, T_3 (Cytomel, Smith Kline & French), methylphenidate (Ritalin, Ciba), or neuroleptics.

TCA'S AND MAOI'S This combination is reported to be particularly effective in refractory patients and may be particularly beneficial in patients with severe anxiety. With regard to safety, it is well within an acceptable range. Recent findings indicate that this combination may decrease the risk of hypertensive crises due to amine reuptake blocking properties of the TCA. The recommended approach is to discontinue previous medications 1 to 2 weeks prior to starting low doses of the TCA (AMI, trimipramine, or perhaps doxepin). Phenelzine is then added to the regimen 2 to 3 days later. Dosages of both drugs should be increased concurrently depending on clinical response or side effects. In the author's experience, for patients already being treated with a TCA, discontinuation may not be necessary. A MAOI can be added in gradually increasing doses under close clinical supervision. At times, it may be necessary to decrease the TCA dose to avoid disturbing side effects, such as orthostatic hypotension and sedation.

TCA'S AND LITHIUM The value of this combination has been supported by a number of clinical studies that indicate that lithium potentiates the antidepressant efficacy of TCA's in refractory patients, possibly resulting from their presynaptic and postsynaptic enhancing effects, respectively, on the 5-HT system. Recently, the same combination has been found effective in a limited number of delusional depressive patients who are unresponsive to combined neuroleptic-TCA treatment. This combination should be considered for bipolar depressed patients not only because this group may not respond to TCA's but also, particularly, because TCA's may precipitate manic episodes. A combination of lithium and MAOI's has also been reported to result in rapid recovery in MAOI nonresponders.

TCA'S WITH T_3 Several open clinical trials have indicated therapeutic efficacy of combining one of the TCA's with T_3 (25 to 50 ng) for the treatment of refractory patients, regardless of sex or polarity of depression. These findings have recently been substantiated under double-blind conditions.

TCA'S WITH METHYLPHENIDATE In addition to its effects on TCA plasma level, methylphenidate also has mood-elevating properties, probably related to its ability to release catecholamines and to block their reuptake. In fact, such psychostimulants as methylphenidate have been reported to be useful in the treatment of selective cases of refractory depression in the elderly. Further research is needed to identify the particular patient subgroups, if any, for whom the use of psychostimulants is indicated.

TCA'S AND NEUROLEPTICS This combination is primarily indicated for delusional depressions.

In addition, several other combinations have been proposed, including MAOI's with L-tryptophan (Tryptacin, OLC), clomipramine (Anafranil) with 5-HTP, and reserpine (Reserpine, Schein), to mention a few. Because there is limited information available concerning these combinations, it is felt that they should be regarded as experimental and, as yet, should not be administered in routine clinical practice.

SIDE EFFECTS OF ANTIDEPRESSANTS A number of undesirable effects have been associated with most antidepressants. These effects are caused by pharmacological properties of these compounds and are probably related to the pronounced action of these drugs on the different neurotransmitter mechanisms, especially at the receptor sites, mainly cholinergic, adrenergic (α-1 and -2) and histamine (H_1 and H_2). Preclinical studies have suggested that the differential effects of some of these drugs on neurotransmitter systems are translated into distinct side effect profiles that may have some significance in clinical practice. These findings should be viewed with caution because they emanate from in vitro experiments, the same drug may simultaneously affect several neurotransmitter and receptor sites to different degrees, and they have not yet been corroborated in well-controlled studies.

Most side effects are benign and transient; they do not always correlate with plasma level or dose. Tolerance frequently develops within 1 to 2 weeks and seems to be directly proportional to the degree of depression. Quite often, the side effects cannot be distinguished from the symptoms of depression, and therefore, the type and intensity of side effects should routinely be checked prior to active treatment.

Special attention should be paid to the elderly, because the risk of developing side effects is increased in this group. This increase is usually attributed to the increased prevalence of underlying diseases in the older age group. In addition, age-related changes in drug metabolism and elimination play an important role in TCA toxicity. These changes range from a substantial decrease in the rate of metabolism, possibly due to decrease in liver mass and hepatic enzyme activity, and an almost 50 percent reduction in renal clearance resulting from vasoconstriction in renal vasculature, decrease of total renal tubular mass, and a decreased cardiac output as a consequence of advanced age. Furthermore, TCA's as highly lipid-soluble drugs can be accumulated in the increased fat depots in the elderly, resulting in prolongation of their action. Finally, the decreased plasma levels of circulating protein may substantially decrease the plasma-protein binding capacity, resulting in higher concentrations of the active, unbound-to-protein portion of the drug. In view of these metabolic changes, plasma concentrations of TCA's can reach very high levels despite moderate oral doses. In fact, it has been shown that SS levels for IMI, AMI and, DMI increase with age. SS levels for NT probably also increase with age, despite previous reports to the contrary. Because of these changes, a lowered dosage should be utilized initially, and it should be increased very gradually.

Issues related to side effects should be discussed with the patient. Such discussion seems to increase compliance and influences the subjective experience of the side effects, making them more tolerable. Reassurance about their transient nature, lowering the dosage, changing to another antidepressant, providing for symptomatic relief of persistent side effects, all assist the patient in complying with the regimen as prescribed.

Cardiovascular Cardiovascular side effects, mainly of TCA's, have been overemphasized. This overemphasis may be due to several case reports of sudden death and dangerous arrhythmias in patients treated with TCA's. Subsequent, well-

designed prospective studies have provided lucid clarification regarding the safety of TCA's, even in high-risk depressed populations, e.g. the elderly or patients with chronic cardiovascular disease. The incidence and severity of cardiovascular effects are probably similar for all TCA's. A possible exception may be nortriptyline, which seems to have fewer orthostatic effects. The claims for decreased cardiovascular effects of the MAOI's, as well as for the second generation antidepressants—amoxapine, trazodone, maprotiline—must be validated in comparative, controlled studies, especially in high-risk groups.

ORTHOSTATIC HYPOTENSION The most common and potentially dangerous (i.e. falls, fractures, lacerations) side effect of TCA's is orthostatic hypotension. Several studies have shown that about 20 percent of patients experience pronounced orthostatic hypotension, averaging up to 25 mm Hg reductions in systolic pressure. So far, the best clinical predictor of this condition in individual patients is the degree of orthostatic drop prior to treatment. Orthostatic changes that are greater than 15 mm Hg strongly suggest that a greater fall will occur after treatment. Postural hypotension seems to be unrelated to sex and age, although elderly or patients with cardiovascular disease, especially impaired left ventricular function (LVF), are at greater risk than noncardiac patients. Orthostatic effects appear to be unrelated to plasma level or dosage, and therefore, dosage readjustments do not usually effect orthostatic changes. Interestingly enough, NT seems to cause much less postural hypotension.

The underlying mechanism of action of the hypotensive effect is not clear. Based on clinical studies, it seems unlikely to be related to α_1-adrenergic receptor or to serotonin reuptake blockade.

EFFECT ON HEART RATE, ELECTROCARDIOGRAM (EKG) RHYTHM, AND CONTRACTILITY Palpitations and tachycardia have been associated with most TCA's. Significant increases in heart rate during treatment with AMI or NT have also been reported, although some recent studies utilizing 24-hour Halter EKG recordings found only trivial increases for IMI.

Along with the type I antiarrhythmic drugs, such as quinidine (Sulfate, Lilly), TCA's are antiarrhythmic and tend to delay conduction. Their action in the specialized ventricular conducting system and ventricular muscle results in moderate increases of PR, QRS, and QTc (QT/RR) intervals, and at times in T-wave amplitude. Prolongation of the PR interval is due to conduction defect in the H-V interval—time from activation of the bundle of His to the activation of ordinary ventricular muscle—whereas the A-H interval is normal.

The clinical significance of these effects depends primarily on the underlying condition of the cardiovascular system. At therapeutic concentration, these effects become clinically significant only in patients with conduction disease, such as A-V block, sinus node disease, or bundle branch disease. In the majority of cases of ventricular arrhythmia, imipramine has been reported to be very effective in reducing premature ventricular contraction.

At therapeutic levels, TCA's have a negligible effect on the mechanical performance of the heart; however, their long-term effects in patients with advanced heart disease require further investigation.

Although TCA's in overdose can be lethal, at therapeutic concentrations they have negligible cardiovascular effects in healthy individuals. Preexistent postural hypotension and conduction disturbances are usually exacerbated by TCA's, although careful monitoring and conservative doses can minimize the risk. PR and QRS intervals are very well correlated with TCA plasma levels and can provide an excellent guide during treatment or in cases of suspected toxicity. QRS duration equal to or greater than 100 msec is indicative of severe toxicity. If severe conduction abnormalities appear, such as sick sinus syndrome, pacemaker insertion may be necessary.

Anticholinergic Anticholinergic side effects are troublesome and can precipitate serious medical problems. Dry mouth, constipation, and loss of visual accommodation (blurred vision) are among the most frequently occurring symptoms. More advanced anticholinergic effects may result in urinary retention, paralytic ileus, or, occasionally, precipitate narrow-angle glaucoma. Central anticholinergic toxicity can occur, even at therapeutic levels, in vulnerable individuals—the elderly, patients with underlying central nervous system (CNS) disease, and slow metabolizers—especially when they are given in combination with antiparkinsonian drugs or phenothiazines with high anticholinergic profile. The toxic syndrome is characterized by confusion, disorientation, delirium, auditory and visual hallucinations, agitation, hyperpyrexia (usually mistaken as infection), and concomitant anticholinergic symptoms. The toxicity can be treated by lowering the dosage. At times, physostigmine salicylate (Antilirium, O'Neal), 1 to 4 mg IV every 3 to 4 hours until improvement is observed, has dramatic results.

The anticholinergic effects of TCA's, most pronounced for AMI and protriptyline (Vivactil, Merck Sharp & Dohme), are probably related to their antimuscarinic properties. In most cases, they can be prevented by choosing an antidepressant with low affinity for muscarinic receptors, such as DMI, NT, or some of the second generation antidepressants, e.g. maprotiline or trazodone. The latter drug seems to have the lowest anticholinergic activity.

Sedative The majority of antidepressants have sedative properties, causing fatigue, decreased energy, lassitude, and hypersomnia, although the degree of sedation varies depending on the particular drug. AMI and doxepin are the most potent, IMI has moderate potency, and DMI is the least active. Most of the time, a reasonable accommodation is possible by gradual dosage increase and avoidance of concurrent sedative-hypnotics or alcohol. Sedation can be mitigated by switching to a less sedating drug like NT or DMI or by providing a single daily dose at night.

In vitro experiments have indicated that these effects are probably related to histamine H_1 antagonism. The significance of these findings should not be uncritically extended to clinical practice. In fact, double-blind studies indicate that trazodone has a greater sedative effect than imipramine.

Central nervous system CNS effects are rare, but they do occur, especially at concentrations above the therapeutic one. These effects can range from a parkinsonian picture to tardive dyskinesia and seizures, particularly in the elderly, children, and alcoholics. Other reported effects include dysarthria, speech blockage, ataxia, and peripheral neuropathies, as well as a fine tremor (usually in the upper extremities). A switch to mania may occur in about 10 percent of the patients recovering on TCA's or MAOI's, even when the previous course was unipolar. Most side effects are often mitigated by dose reduction. For full-blown manic episodes, lithium is usually effective. In a few cases of persistent tremor, propranolol (Inderal, Ayerst) may be helpful.

Of the second generation antidepressants, maprotiline has more frequently been reported to be associated with convulsions as compared to TCA's. The risk of seizures appears to be dose related, greater with daily doses above 150 mg/day.

Similarly, an increased number of reports of galactorrhoea and hyperprolactinemia have been associated with amoxapine. These effects are probably related to its dopamine-blocking action. Further studies are needed to clarify the clinical importance of both these findings.

Miscellaneous side effects Most psychoactive drugs, including antidepressants, have been implicated in weight gain. This effect may be due to increased appetite on recovery or to unknown central effects. A diet program seems to be the most effective antidote.

Skin rashes, probably allergic, sometimes occur in the form of urticaria and photosensitivity. The rashes have been more frequently reported—4 to 5 percent—with maprotiline. Agranulocytosis is extremely rare, but has been reported for AMI, dothiepin, IMI, and mianserin.

Impaired orgasm (both sexes), as well as delayed and sometimes painful ejaculation, has frequently been reported with TCA's, MAOI's, and, more recently, with the newer antidepressants, such as amoxapine. The mechanism of action of these effects is not known; they seem to be related both to dose and individual sensitivity. Dosage reduction may be helpful; otherwise, a switch to another antidepressant may be necessary.

Peripheral edema may be observed in elderly patients during treatment with MAOI's and is probably due to excessive secretion of antidiuretic hormone. This edema is unresponsive to diuretics and may necessitate switching to another antidepressant.

Withdrawal effects, following abrupt cessation of TCA's, have occasionally been reported. They include nightmares, insomnia, vertigo, gastric distress, and irritability. At times, manic episodes have occurred; therefore, gradual withdrawal is advisable.

ANTIDEPRESSANT OVERDOSE One of the gravest consequences of TCA treatment is accidental or deliberate overdose. Quantities greater than 1.25 g can be lethal. Although coverage of all aspects of TCA overdose is beyond the scope of this section, the clinician should be familiar with some important clinical and therapeutic principles. Major clinical manifestations of overdose include (1) myoclonic jerks or chorioathetoid movements or both without seizure EEG activity (pseudoconvulsions); (2) agitation and frank delirium, gradually progressing to coma and metabolic acidosis; (3) hyperpyrexia neuromuscular irritability and seizures; (4) internuclear ophthalmoplegia with intact pupillary, and, at times, corneal responses and no abnormal motor signs of posturing or quadriparesis (most frequently reported with AMI and doxepin); (5) paralytic ileus; and (6) a plethora of cardiovascular manifestations—mainly, severe hypotension, atrioventricular and intraventricular conduction disturbances, and arrhythmias, particularly ventricular arrhythmias.

At the present time, there are no specific guidelines or antidotes for routine management of overdose. Every case is best handled on an individual basis and in an intensive care unit, where the patient should be treated by an expert cardiologist and should receive ventilatory assistance, as well as appropriate supportive care. Gastric lavage may be helpful within the first 12 hours. Instillation of activated charcoal may bind the drug, and continuous aspiration may reduce delayed toxic effects. Hemodialysis is futile because most of the drug is bound to plasma proteins.

CNS symptoms, including pseudoconvulsions, may be reversed by physostigmine, 1 to 2 mg IV every 3 to 4 hours; however, caution should be exercised because, at times, physostigmine may exacerbate heart block and induce bradycardia and hypersalivation (cholinergic effects).

Management of cardiovascular manifestations is extremely difficult. Continuous cardiac monitoring, with provision for resuscitation, and detailed assessment of hemodynamic status (intrapulmonary catheterization) are the cornerstones of adequate care. Electrolytes and arterial blood gases also need to be monitored in order to correct hypocalcemia or acidosis. The arrhythmias are similar to those seen in quinidine toxicity, and should be managed with sodium lactate or pacing or both. Type I antiarrhythmic drugs like quinidine or procainamide (Pronestyl, Squibb) are contraindicated. Phenytoin (Dilantin, Parke-Davis) 50 mg/min up to 2 to 5 mg/kg, as well as lidocaine (Lidocaine, Abbott) and propranolol, have been used quite successfully. If arrhythmias are still nonresponsive, then one may try bretylium tosylate (Bretylol, American Critical Care) 1.5 mg/min. Hypotension secondary to bretylium would best be treated with simultaneous norepinephrine bitartrate (Levophed Bitartrate, Breon) infusion.

Seizures may respond to phenytoin infusions. If not, diazepam (Valium, Roche) may be helpful, although it can aggravate CNS respiratory depression. Hyperpyrexia can be treated by cooling.

Recovery from overdose is usually evidenced by clinical signs, normalization of plasma levels, and EKG (QRS returns to normal).

Experience with the management of MAOI or second generation antidepressants overdose is limited. Although patients who may overdose on second generation drugs may exhibit many of the symptoms seen in TCA overdose, cardiac arrhythmias have been less frequently observed.

Regardless of drug, supportive measures are usually the same; however, in MAOI overdose, administration of sedatives with α-adrenergic receptor blocking action, such as chlorpromazine and muscle relaxants, may be helpful.

MANIA

SELECTION OF PATIENTS A complete evaluation of patients presenting with symptoms of mania—listed in DSM-III as bipolar affective disorder, currently manic—is accomplished by obtaining a detailed history, a thorough medical-neurological examination, and a careful psychiatric work-up. The appropriate selection of patients for pharmacological treatment of mania rests on astute diagnostic skills. The clinician should recognize that this syndrome is not synonymous with the normal mood states of elation, euphoria, anger, or irritability. Even when mild to moderate hypomania is present, pharmacotherapy may be unnecessary. Quite often such states are ego-syntonic, productive, and conducive to creativity. Secondary manias are manifestations of a variety of CNS disorders and can be precipitated by psychostimulants and illicit drugs; a reliable diagnosis is essential to treatment decisions. Experienced clinicians are aware of the difficulties involved in differentiating schizoaffective, as well as schizophrenic, disorders and mania. Perhaps in reaction to the tendency of American psychiatrists to overdiagnose schizophrenia, the DSM-III asks the clinician to accept even mood-incongruent delusions or hallucinations as a possible part of the symptom constellation in some manic episodes. Aside from the diagnostic significance of this issue, which the author considers to be, at least, controversial, the presence of psychotic symptoms should not interfere with the clinician's recommendations for pharmacotherapy. Presenting symptomatology, exclusive of longitudinal perspective, can be misleading. Accumulated clinical and research experience indicate that the best clinical predictors of positive treatment

outcome in mania are (1) family history of affective illness, (2) cyclicity with normal interepisodic function, and (3) satisfactory premorbid adjustment (absence of personal or intellectual deterioration). Therefore, the clinician's recommendations for or against treatment with lithium should be based solely on clinical judgment, guided by the above factors. Considerations should include (1) the severity and duration of the present episode, (2) past history of drug response, and (3) the possible effects on the patient's social and occupational functioning.

The next crucial decision involves choosing the appropriate treatment setting. The patient's social support system, history of behavior during prior episodes, predilection to violent acting out, and willingness to cooperate with the treatment plan should all be considered. Opinions of family members should be obtained and will often weigh heavily for or against outpatient management. Some of the most meaningful pharmacotherapeutic approaches will now be delineated, highlighting the basic principles of appropriate management in mania.

EFFECTIVE TREATMENTS Lithium LITHIUM VERSUS NEUROLEPTICS Lithium and neuroleptics are currently considered to be the most appropriate pharmacological approaches for treatment of the manic phase of manic-depressive illness (MDI). In well-controlled, double-blind studies, both agents were found superior to placebo, with a therapeutic success rate approaching 80 percent. Debate continues, however, concerning the comparative efficacy of lithium and neuroleptics. Based on a previous critical review of the state-of-the-art and clinical experience in this area, lithium carbonate should be considered the treatment of choice for this condition. It has several advantages over neuroleptics, including a greater degree of specificity and ease of monitoring through plasma levels. In addition, lithium lacks the stigma associated with the antischizophrenic drugs and does not produce tardive dyskinesia or sedation. From the patients' perspective, therefore, it is a much more acceptable drug. It should be noted, however, that lithium has a slower onset of action—that is, a 7 to 12 day lag period—which may be a disadvantage in the treatment of highly disturbed manic patients. Most experts favor treating these cases with a combination of lithium and neuroleptics until the desirable behavioral control is accomplished and the patient can be safely managed on lithium alone. The possible, although remote, dangers of such a combination include neurotoxicity, especially with haloperidol (Haldol, McNeil), decreased renal concentrating capacity, and some rare somnambulistic-like phenomena. Therefore, close clinical observation for early signs of neurotoxicity or nephrotoxicity or both is highly advisable. With these precautions, the combination of lithium with neuroleptics for acute and violent cases of mania is safe and highly indicated. In the few cases where this combination is not tolerated, clonazepan (Clonopin, Roche), an anticonvulsant that increases 5-HT synthesis, may be used in dosages of 2 to 4 mg four times daily. Recent studies with a limited number of patients indicate that this drug is rapidly acting, highly sedating, and well tolerated in the control of acute mania.

LITHIUM PREPARATIONS In the United States, most lithium products are either rapidly absorbed or slow-release preparations. The conventional lithium carbonate is rapidly absorbed, with peak serum levels of approximately 1.5 hours. Eskalith CR (450 mg of lithium carbonate) and Lithobid (300 mg of lithium) are similar slow-release preparations, with peak serum levels of approximately 4.5 hours, and may be used in cases where compliance or disturbing side effects, such as tremor and nausea, due to frequent dosing become a problem.

CLINICAL PHARMACOLOGY AND PRETREATMENT WORK-UP Prior to the initiation of lithium treatment, the physician must be thoroughly familiar with the pharmacological properties of the drug and the medical status of the patient.

Lithium is an alkali metal similar to sodium, potassium, magnesium, and calcium. Following ingestion, it is completely absorbed by the gastrointestinal tract. Serum levels peak in 1.5 to 2 hours with lithium carbonate, or they peak in 4 to 4.5 hours with a slow-release preparation. Lithium does not bind to plasma proteins and is distributed nonuniformly throughout body water. It reaches equilibrium after about 5 to 7 days of regular intake. Lithium has an elimination half-life of almost 24 hours. Although nonsignificant losses occur through the skin or in the feces, about one-fifth of the lithium ion is eliminated through renal excretion during each circulatory cycle of the kidneys. This process is dependent on glomerular filtration rate (GFR) and sodium balance, and it varies considerably as a function of fluctuations in these parameters. Lithium is reabsorbed primarily in the proximal tubules together with sodium, although the loop of Henle (ascending limb) and the distal nephron may play some role. A decrease in plasma sodium levels, resulting from diuretics, excessive sweating, and reduced sodium intake, initiates a compensatory increase in sodium reabsorption accompanied by lithium reabsorption.

Considering these pharmacological properties, as well as the well-known potential of lithium to adversely affect the CNS, thyroid, heart, and kidneys, it is necessary that candidates for lithium undergo a thorough physical examination, in which particular attention is given to the evaluation of the above systems. Aside from well-functioning kidneys, there are no absolute contraindications to lithium therapy. Sound clinical judgment and close monitoring should be exercised, however, whenever clinical status is complicated by cardiovascular problems, conditions affecting fluid and electrolyte balance, general anesthesia, and concomitant administration of other drugs. In such cases, lithium is as safe as other psychotropic drugs and should be used at substantially reduced dosage only if absolutely indicated. For patients in reasonably good health, medical work-up should include a routine physical examination; EKG; laboratory test, including urinalysis; SMA-12; complete blood count; drug serum creatinine, and BUN, as well as thyroid-stimulating hormone (TSH). A 12-hour specific gravity test should also be considered as an additional precaution. Twenty-four-hour urine volume and GFR with creatinine clearance are recommended. The collection of urine should be adequately supervised and complete.

BEGINNING TREATMENT Placing a patient on lithium should be preceded by an initial dosage determination. Wide variability exists among patients in the dosage required to attain therapeutic plasma levels. Individual dosage requirements can be more accurately determined based on plasma lithium concentrations 24 hours after taking a test dose of 600 mg of lithium carbonate. During the initial period, this method does not replace frequent plasma determinations, which usually are made twice in the first week and then once a week. Plasma levels should be drawn in a standardized manner. This process is accomplished by drawing a blood sample 12 hours after the evening dose, provided that the patient has been taking the same divided daily dosage of lithium, reliably, for about 1 week. On stabilization of the acute phase, plasma levels should be determined at progressively longer intervals, unless otherwise indicated by deterioration, toxicity, concomitant intake of thiazide diuretics, loss of salt, or impaired kidney function. For elderly patients, it may take more than 1 week to reach steady-state levels, due to the longer elimination half-life (about 36 hours); therefore, levels should be drawn about 10 days after the last dosage readjustment, unless there is concern for toxicity.

Regarding optimal therapeutic level, it should be kept in mind that knowledge in this area is still incomplete. Optimal

levels vary from individual to individual, and the physician should be guided primarily by the patient's clinical state or the development of side effects or both. Usually levels below 0.4 meq/l have not been associated with therapeutic response, whereas levels above 1.5 meq/l have been frequently associated with side effects. This response is extremely variable, however, and very low levels of lithium have been known to produce side effects. Based on a large number of studies, most of them retrospective, the recommended therapeutic range for the acute phase is approximately 0.8 to 1.8 meq/l, although deviations from this range, either below or above, have been utilized quite successfully.

For the average healthy young adult in a manic episode, a dosage of 600 mg, three times daily, is recommended as the usual starting dose. Because present knowledge regarding optimal levels is limited, an appropriate dosage schedule should always be determined on the basis of severity of the clinical condition, body weight, age, concurrent illness, and medication, as well as kidney function. The usual dosage range is between 900 and 2100 mg/day, although, at times, higher doses have been employed for extremely severe cases of mania, without subsequent disturbing side effects. For severely disruptive behavior, intramuscular administration of neuroleptics at frequent time intervals is often considered preferable in order to attain rapid behavioral control and stabilization of the clinical condition. Following stabilization, the neuroleptic, usually haloperidol or chlorpromazine, should be given orally, preferably in liquid form, to prevent eventual covert disposal of the drug by the patient. When the effects of lithium become apparent, the neuroleptic should be gradually discontinued.

DISCONTINUATION OF TREATMENT Gradual withdrawal of lithium may be indicated in certain patients who have recovered from a manic episode and have been in stable condition for at least 5 to 6 months. Discontinuation may be especially warranted if there is no prior history of affective disorder or if prior episodes had insidious onsets, rather than acute ones, were not severe, and were separated by extensive intervals of normal functioning. Such patients should always be informed of the possibility of recurrence, which may even follow a long symptom-free interval. Medication should be tapered, because abrupt withdrawal may precipitate a manic or depressive response. The majority of patients do not experience withdrawal or rebound phenoma.

SPECIAL CONSIDERATIONS ELDERLY The general outlines above are applicable to the elderly, with some special considerations. In view of the longer elimination half-life found in elderly persons, these patients are at greater risk for toxicity and require less lithium, usually 900 mg daily, to achieve therapeutic levels.

PREGNANCY Due to the potential teratogenic effects of lithium, mainly cardiovascular, it should be discontinued during the first 3 or 4 months of pregnancy. In cases of severely disturbed manic patients, this decision should be thoroughly explored with the family in an informative and supportive manner. For the remaining time, lithium, if absolutely indicated, should be reinstituted and readjusted accordingly (increase intake) in view of the substantial increases in GFR, plasma volume, renal plasma flow, and tubular sodium reabsorption occurring during pregnancy.

Lithium dosage has to be decreased or even discontinued for a few days before and after delivery so that toxicity following postpartum decreases in the GFR may be avoided. Close clinical and laboratory monitoring should be continued following delivery. Breast feeding should be strongly discouraged because lithium is excreted in the mother's milk—10 to 50 percent concentration in maternal serum—and because there is limited information regarding its effects on the systems of the developing infant. Whenever discontinuation of lithium is unavoidable, a strong therapeutic alliance that is based on the treating physician's genuine concern and consuming commitment to the patient is instrumental in successfully maintaining the patient free of relapses throughout critical periods. This alliance applies, of course, to other problematic cases, such as fragile, elderly, and resistant patients.

NEGATIVE FLUID BALANCE Due to lithium's well-known potential to lower renal concentration, with resulting polyuria, polydipsia, and fluid loss, it is essential that patients drink plenty of fluids and have their serum lithium levels closely monitored. Under circumstances during which negative fluid balance is likely to occur, such as during presurgery and postsurgery, fluids should be given intravenously under close medical monitoring.

REFRACTORY MANIAS Treatment failures usually range between 20 and 40 percent. These nonresponders cannot be easily identified on clinical or biochemical grounds. Nevertheless, several factors have been implicated, including family history, inadequate dose, low plasma lithium levels, previous failure of lithium treatment, rapid cycling (four or more episodes of mania per year), and diagnosis (schizophreniform features). Presenting symptomatology is not always a very reliable predictor of clinical response. It seems more likely that the course of illness and a family history of affective disorders have a better predictive capacity than the manifest symptomatology. Generally, patients are considered to be nonresponders after at least 2 weeks of adequate plasma lithium levels, usually above 1.2 meq/l. In such cases, scrupulous evaluation of the above factors should be the initial step in examining the possible reasons for failure. Additionally, review of the patient's history and a physical examination may reveal the causes of secondary mania. These causes include drugs (steroids, L-dopa), infection (Q fever, influenza), and neoplasms. Hospitalization may be considered at this point to check for nephrogenic diabetes insipidus (NDI). A 24-hour urine collection, greater than 3000 ml, is highly suggestive of this entity. NDI may predispose to a poor outcome with lithium therapy. If NDI is present, administration of thiazide diuretics (Hydrodiuril, Merck Sharp & Dohme), 25 to 50 mg orally once daily, should correct the NDI and also enhance lithium response. This treatment must be rigorously supervised by monitoring side effects, lithium levels, and electrolytes. The dosage of lithium may require adjustment to maintain levels below 1.5 meq/l. Likewise, potassium supplementation will depend on serum electrolyte determinations. If NDI is not present, lithium levels should be raised from 1.5 to 2.0 meq/l. This increase may convert a patient into becoming a lithium responder. Of course, these methods require thorough understanding of lithium's side effects, close clinical and laboratory supervision, and, preferably, should be administered in a hospital setting. If, despite the above measures, the patient is still not responding or if hospitalization is not possible, neuroleptics alone or in combination with lithium should seriously be considered. In most cases, the addition of haloperidol or chlorpromazine in gradually increasing dosages will bring most manics under control. Gradual tapering of neuroleptics should be attempted only after a stable satisfactory recovery has been accomplished. If

resistance to treatment continues, additional alternatives should be considered. Carbamazepine (Tegretol, Geigy), an approved anticonvulsant drug, has been found effective in refractory cases of mania. Clorgyline, a selective MAO-A inhibitor, and levothyroxine sodium (Levothroid, Armour) have been reported to be effective treatments in a limited number of intractable "rapid-cyclers." Unlike carbamazepine, however, the efficacy of the latter two drugs has not yet been tested in well-controlled studies. Finally, in the exceedingly rare cases of continued nonresponse following the above interventions, ECT can be utilized; this therapy has been widely held to be clinically effective.

SIDE EFFECTS AND TOXICITY OF LITHIUM TREATMENT Lithium is not an innocuous drug; it has a variety of systemic side effects, primarily on the CNS, thyroid, and kidneys.

Central nervous system effects The effects of lithium on the CNS vary and range from mild to severe. The least harmful and usually reversible effects include anxiety, fatigue, lassitude, lethargy, tension, impaired concentration, mild cognitive and memory impairment, decreased motor performance, muscular weakness, and tremor. The progressively more severe and, at times, life-threatening effects occur in cases of generalized neurotoxicity. These effects include impaired consciousness, muscular fasciculations and twitching, extrapyramidal symptoms, coarsening of hand tremor, visual disturbances, and seizures.

Mild CNS effects usually appear during the initiation of treatment and are seemingly dose-related. They usually subside with gradual dosage increase, reassurance, frequent dosing, or administration of a slow-release preparation. The most common (about 50 percent) and unpleasant of these side effects is a fine intention tremor of the hands, which occurs more frequently in males. It is intensified by social stress and caffeine, is usually attenuated by sedatives, and is not relieved by antiparkinsonian drugs. If the tremor does not improve with time and the above measures do not help, it may be necessary to lower the lithium dosage. Often, in resistant cases, 10 to 40 mg of propranolol three times daily, or diazepam, will suppress the tremor.

Severe CNS effects of lithium usually indicate serious toxicity. Toxicity can occur at normal therapeutic ranges and often confuses the clinician into thinking that the patient is becoming manic. Raising the dosage could be a serious mistake under such circumstances. Close observation and clinical evaluation will minimize this possibility. The toxic manifestations encompass a broad range of neurological symptoms. Confusion, poor concentration, and clouding of consciousness can progress to frank delirium and coma. Ataxia, dysarthria, and nystagmus are cerebellar findings in lithium toxicity. Hyperactive reflexes and fasciculation are also reported. The final sequelae of severe intoxication can be convulsions, status epilepticus, and even death.

Any change in mental status during lithium treatment warrants careful clinical evalution, including neurological examination, serum electrolytes, EKG, possible EEG, and plasma levels. Familiarity with the toxic symptoms, however, should enable the clinician to discriminate between mania and intoxication. In the majority of intoxication cases, withdrawal of medication and symptomatic treatment provide visible results within the first 24 hours. For severe intoxication, hemodialysis is the treatment of choice and should not be delayed, considering the risk of irreversible brain damage and impending death. Accumulated evidence indicates that preexisting organic brain damage, dementia, and schizophrenia predispose to CNS side effects of lithium.

Cardiac effects The cardiac effects of lithium resemble hypokalemia on EKG. This similarity is due to displacement of intracellular K+ by the lithium ion. The most common changes on EKG are T-wave flattening or inversion. These changes are of a benign nature, and they disappear after excretion of lithium from the body; nevertheless, baseline EKG's are essential and should be repeated during maintenance. In rare cases, sinus and atrioventricular nodal arrhythmias, ventricular arrhythmias, edema, and congestive heart failure have been associated with lithium therapy. In cases of toxicity, more serious EKG changes appear, such as reversible first-degree atrioventricular (A-V) block, intraventricular conduction delays, prolonged Q-T interval, and circulatory failure, necessitating EKG monitoring in cases of suspected lithium toxicity.

Thyroid effects Lithium also affects thyroid function, causing a generally benign diminution in the concentration of circulating thyroidal hormones. Reports of goiter (5 percent), benign reversible exophthalmus, and hypothyroidism (3 to 4 percent) have also been attributed to lithium. About 50 percent of patients on chronic lithium treatment have abnormal thyrotropin-releasing hormone (TRH) response, and approximately 30 percent have elevated TSH. If laboratory values of thyroid hormone indicate dysfunction, then supplementation can be administered safely. Initial TSH levels are indicated and should be repeated periodically. Hyperthyroidism has rarely been reported.

Dermatologic effects Several cutaneous side effects, which may be dose dependent, have been associated with lithium treatment. The more prevalent effects include acneiform, follicular and maculopapular eruptions, pretibial ulcerations, and worsening of psoriasis. Most of these effects respond to the usual dermatologic measures; however, worsening of psoriasis and, at times, acneiform eruptions, may require discontinuation of lithium. Concurrent administration of tetracycline may precipitate lithium toxicity.

Renal effects The nephrotoxic potential of lithium has been well documented in several studies. In acute lithium intoxication, primarily a CNS syndrome, patients develop reversible tubular disturbances commonly associated with high plasma lithium concentrations. Chronic nephrotoxicity may develop following prolonged exposure to lithium, even when the plasma levels are within the usually accepted therapeutic range. Of the two major renal functional systems, tubular function is the most frequently affected, whereas glomerular function is affected to a much lesser extent. Morphological changes leading to irreversible renal damage have recently raised additional concern.

Renal tubular defects usually occur in 10 to 50 percent of patients receiving prolonged treatment with lithium. These deficits have been attributed to lithium's inhibition of the antidiuretic hormone (ADH)-adenylate cyclase interaction in the renal tubular epithelia. Clinically, the deficits are manifested as polyuria (24-hour urine volume of more than 3 l) and polydipsia, and they appear to be dose dependent, benign, and reversible. A substantial number of long-term lithium patients develop impaired renal concentrating ability, which occasionally progresses to a frank NDI, and compensatory fluid intake. These side effects may persist for some time after discontinuation of treatment and, although bothersome, can

be managed by dosage reduction and, perhaps, a single daily dose schedule. Thiazide diuretics, paradoxically, are very effective. Patients should be instructed to drink a great deal of water, but not high calorie beverages, especially during periods of increased risk for negative water balance, e.g. heavy sweating, fever, and major surgery. Glomerular function is insidiously affected to a moderate degree in less than 10 percent of patients on long-term lithium, indicating that the risk of renal insufficiency is small, even in long-term lithium treatment. There are few reported cases of lithium-induced nephrotic syndrome—hypoalbuminemia, proteinuria, edema, and hyperlipidimia—at therapeutic levels. These rare complications, of unknown etiology, are reversible. Renal morphological changes, mainly interstitial fibrosis and tubular atrophy, resembling interstitial nephritis, have been reported in 10 to 20 percent of patients on long-term lithium treatment. These findings have been criticized on the grounds that the relevant studies were retrospective and cross-sectional in design, they employed no appropriate controls, and they involved only fragmentary data on renal function predating lithium therapy. Subsequent studies, employing control groups, have shown significantly more nephropathy in patients given lithium than in healthy controls (kidney donors), but have shown an equal degree of nephropathy when compared with an affective illness control group not taking lithium. These results imply that affective disorder patients may be at greater risk for developing renal morphological changes.

At present, it is conceivable that several factors are implicated in glomerular and tubular function defects, including preexistent renal pathology, high plasma lithium levels, and multiple dosing. Affective illness, per se, and concomitant treatment with other drugs may also be associated with changes of kidney morphology and need to be examined in prospective studies. Meanwhile, careful assessment of these factors, combined with rigorous pretreatment clinical and laboratory screening and close monitoring of the patient during the whole treatment period, should be essential requirements for sound lithium treatment.

LONG-TERM TREATMENT

Recent advances in the diagnosis and classification of affective disorders, combined with improved knowledge of the natural course of the disease process, have contributed to the present understanding of the value and problems associated with maintenance treatment. It has long been recognized that affective disorders are episodic. Bipolar episodes usually last for about 4 months, whereas for unipolar patients the duration of an episode is about 4 to 8 months. Episodes are more frequent for bipolar patients (around 8) than for unipolar patients (5 to 6), and the frequency of episodes is greatest during the first 10 years of illness.

The decision regarding initiation of maintenance treatment should be carefully made, based on a number of considerations. Candidates are patients whose histories show recurrent affective episodes of sufficient frequency, duration, and intensity to interfere with their life-styles. Another provision is that the risk-benefit ratio of long-term therapy is carefully estimated, based on an appreciation of the number of relapses anticipated within a given period of time, as well as on the degree of resulting disability. Early relapses are more likely to occur in patients with multiple prior episodes, particularly after an episode preceded by a short symptom-free interval. In older patients, relapse is more probable following the first episode. Another indication of maintenance treatment is sudden affective episode without prodromal signs.

Based on well-controlled studies of the currently available drugs, lithium is the drug of choice for maintenance treatment of bipolar affective disorders. It is also effective in maintenance treatment of unipolar depressions. Antidepressants are clearly effective in maintenance treatment of unipolar depressions and probably are the drugs of choice following recovery from a severe depressive episode. Their dosage should be decreased to the lowest level required for continued efficacy. Usually, this means one-third to one-half less than the dose associated with optimal clinical response during the acute phase. Therefore, the choice of either lithium or TCA's in unipolar depression depends on the severity of the last episode, patients' sensitivity to side effects, and individual preferences to continue on the same drug that had a favorable effect during the acute episode. It should be noted, however, that these drugs are not "preventive or prophylactic" in the true medical sense as, for instance, vaccinations are for infectious diseases. Rather, their effectiveness is analogous to that of insulin or antihypertensives in medicine; that is, they allow patients to live productive lives without serious limitations in their functioning.

There is a wide variation of response patterns to lithium maintenance, a variation that ranges from complete abatement of subsequent episodes to no response at all (20 to 30 percent), with several degrees of intensity and frequency attenuation in between. Useful clinical predictors of positive response include (1) good quality of free intervals, (2) diagnosis of affective disorder, and (3) low frequency of preceding episodes (1 to 2 per year).

Careful selection, limited to lithium-responsive patients, will enhance therapeutic efficacy and will spare patients the potential side effects associated with long-term lithium use (higher frequency in lithium nonresponders). The clinician should explore alternative forms of treatment for bipolar lithium nonresponders. In fact, preliminary data indicate that, although these patients are not successfully maintained on lithium, long-term treatment with carbamazepine is successful. These findings imply that the responders to each drug may comprise a different affective subtype.

Optimum maintenance lithium levels have not yet been determined, although there is evidence that the effectiveness of lower levels (0.4 to 0.6 meq/l) may be equal to that of higher levels (0.8 meq/l) and may be much safer. Ideally, for every individual patient, one should always readjust the dosage to the level that provides maximum protection and safety. There is considerable controversy regarding frequency of daily dosing; nevertheless, it appears that divided doses may be more harmful to kidney structure and function than a single nighttime dose. This outcome is probably due to regenerative processes occurring during low lithium concentrations.

Rapid cyclers are usually less responsive to lithium maintenance therapy. Concurrent use of antidepressants may contribute to this failure. At times, administration of clorgyline may be useful.

In some patients, successful stabilization may take 6 to 12 months. During this period, manic relapses are usually treated by increasing the lithium dose or, if necessary, adding a neuroleptic. Depressive relapses are best handled by temporary administration of antidepressants. If, after 1 year, stabilization is not achieved, alternative treatments should be considered, following gradual dosage reduction and discontinuation of lithium.

Poor compliance is a common factor in the failure of lithium prophylaxis. It has been attributed to various subjective concerns, which the sensitive clinician should gently explore and attempt to allay. For example, there may be

perceived loss of creativity or fears of long-term toxicity. Some patients do not like the idea that they are chronically ill and that their mood is controlled by lithium. Compliance can be improved by a sustained therapeutic relationship; by proper education, supplemented by verbal and written instructions; and by encouraging participation in lithium support groups.

FUTURE OUTLOOK

The search for effective treatments of affective disorders has continued uninterrupted throughout the history of mankind. Despite recent progress, optimal diagnosis and treatment for this common and devastating mental illness have yet to be achieved.

Although revolutionary advances in pharmacotherapy have been instrumental in reducing over-all morbidity and mortality, these potent medications are not, as yet, the final solution to the painful problem of successful management. Most of them are efficacious in certain subtypes of depression, primarily endogenous, but they have several drawbacks. They are ineffective in a great number of depressed patients, have a delayed onset of antidepressant action (usually about 2 to 3 weeks), and have significant side effects that are potentially lethal in cases of overdose. Careful appreciation of these shortcomings, coupled with common sense, sensitivity, sincere concern, modesty, and astute clinical judgment, are absolute prerequisites for optimal treatment.

Much remains to be learned about the etiology, nature, and treatment of affective illness. It is hoped that further research advances in the field will provide more clinical and biological predictors of response to antidepressant treatments, new and safe medications, and will advance present knowledge into the pathophysiology of affective disorders.

SUGGESTED CROSS REFERENCES

The reader is referred to Section 30.2 for a detailed discussion of antidepressant drugs. Convulsive therapies are covered in Section 30.5. Suicide is discussed in Section 28.1. A discussion of the basic science of psychopharmacology is covered in Section 2.2.

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