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EDITORS

HAROLD I. KAPLAN, M.D.

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

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Williams & Wilkins
351 West Camden Street
Baltimore, Maryland 21201-2436, USA
800-638-0672

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CHAPTER 15 OTHER PSYCHOTIC DISORDERS

15.1 SCHIZOAFFECTIVE DISORDER, SCHIZOPHRENIFORM DISORDER, AND BRIEF PSYCHOTIC DISORDER

SAMUEL G. SIRIS, M.D.
MICHAEL R. LAVIN, M.D.

INTRODUCTION

Throughout the 20th century, psychiatry has traditionally categorized the functional psychoses as belonging to one of two basic groups of disorders, either to the group of disorders now known as schizophrenia or to the group of disorders now known as mood disorders. That diagnostic distinction has been based on two arenas of observation: symptoms and longitudinal course. Patients with predominantly perceptual and cognitive problems (hallucinations, impaired reality testing, and thought disorders) and with a deteriorating social or vocational course have come to be classified as having schizophrenia. Patients whose symptoms are predominantly in the realm of a disorder of mood regulation (either in the direction of depression or in the direction of euphoria or irritability) and who tend to have a more fully remitting course have come to be classified as having mood disorders.

That characterization, however, does not work well for all patients encountered in clinical practice. Some patients present with mixtures of those characteristics. That is, some patients have symptoms that have prominent and persistent aspects of both perceptual-cognitive disturbances and mood disturbances. Other patients seem to have predominantly perceptual-cognitive symptoms but have a favorable psychosocial course, with full remission after an episode of relatively short duration. Still other patients present with symptoms that are predominantly in the realm of mood, but the disorders fail to remit or the patients experience deteriorating psychosocial courses. Those observations have led to the hypothesis that a so-called third psychosis exists, and to the alternative formulation that all psychoses are on a spectrum reaching from pure schizophrenia at one extreme to pure mood disorders at the other. Adhering to a nontheoretical approach, the editors of *Diagnostic and Statistical Manual of Mental Disorders* (DSM) have grouped patients with mixed characteristics into the larger and potentially heterogeneous category of psychotic disorders not otherwise specified.

Over time, many patients with prominent or persistent symptoms in both the perceptual-cognitive and affective realms have come to be spoken of as having schizoaffective disorder, a term that itself implies the two notions. However, many definitions of schizoaffective disorder have been used over the years, greatly complicating its conceptualization and the accumulation of an empirical data base concerning patients with the disorder. Indeed, at times the existence of schizoaffective disorder as a proper diagnostic category has been challenged. Nevertheless, the presenting symptoms and histories of a sizable number of patients seem to force the use of the diagnostic category, which the first part of this section considers.

The later parts of the section, concerning schizophreniform disorder and brief psychotic disorder, address those patients whose presenting psychotic symptoms are consistent with schizophrenia but whose remitting courses and favorable psychosocial outcomes do not conform to the typical longitudinal patterns of schizophrenia.

SCHIZOAFFECTIVE DISORDER

DEFINITION Schizoaffective disorder is defined by the fourth edition of DSM (DSM-IV) as a psychiatric illness that includes significant and enduring mood symptoms, thus satisfying criteria that, in the absence of psychotic symptoms, would qualify for a diagnosis of a major mood disorder. In schizoaffective disorder, however, the mood symptoms overlap with prominent psychotic symptoms that are also persistent and that continue to be present during a substantial interval of illness when the patient lacks prominent mood symptoms. However, the symptoms that meet criteria for a mood episode must also be present for a substantial portion of the total duration of active and residual periods of that episode of illness. In addition, if the mood episode is a major depressive episode, pervasive depressed mood must be present. The specific DSM-IV diagnostic criteria are listed in Table 15.1-1.

DSM-IV also specifies the diagnosis of schizoaffective disorder in two ways. It distinguishes between a bipolar type and

TABLE 15.1-1
Diagnostic Criteria for Schizoaffective Disorder

A. An uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia.
   Note: The major depressive episode must include criterion A1: depressed mood.
B. During the same period of illness, there have been delusions or hallucinations for at least two weeks in the absence of prominent mood symptoms.
C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.
D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify type:
Bipolar type: if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes)
Depressive type: if the disturbance only includes major depressive episodes

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

a depressive type on the basis of whether the interval of illness includes a manic or mixed episode (bipolar type) or only a depressive episode or episodes (depressive type).

HISTORY At the end of the 19th century, Emil Kraepelin proposed a two-entity model for functional psychiatric disorders. The elegant simplicity of that model and the massive scholarship underlying it have dominated psychiatric nosology ever since. According to that model, a deteriorating course and an otherwise poor prognosis were intimately linked with dementia precox (later defined as schizophrenia by Eugen Bleuler); a favorable or remitting course of illness was associated with a manic-depressive (that is, mood disorder) diagnosis.

The practical clinical world, however, was not to be divided up that easily; a substantial number of patients did not fit cleanly into one category or the other. The term "schizoaffective" was first used by Jacob Kasanin in 1933 to describe a group of patients with acute psychoses that contained both schizophrenic and affective features. The patients' premorbid functioning tended to be good, their psychotic episodes brief, and their prognoses relatively favorable. Four years later Gabriel Langfeldt, exploring apparently schizophrenic patients who atypically experienced recovery or otherwise good outcomes, coined the term "schizophreniform." That grouping of patients, otherwise thought to have important features of schizophrenia, who experience relatively favorable outcomes persists to this day.

COMPARATIVE NOSOLOGY

DSM-I, DSM-II, and DSM-III The first edition of DSM (DSM-I), published in 1952, continued the tradition of classifying schizoaffective disorder as a subtype of schizophrenia, which was consistent with the tendency to overdiagnose schizophrenia in the United States during the mid-20th century, in comparison with European practices. During the next decade and a half the antipsychotic drugs that were discovered and that began to revolutionize many aspects of psychiatry were often thought of as being antischizophrenic; consequently, the second edition of DSM (DSM-II), published in 1968, made few changes in the diagnostic position of schizoaffective disorder. However, the progressive development of lithium (Eskalith) in the 1960s and the early 1970s as a treatment for mania helped stir a reassessment of the nosological position of schizoaffective disorder. Citing the usefulness of lithium in at least some cases of schizoaffective disorder and the early studies of outcome and family history, several authors began to propose that schizoaffective disorder be classified with affective illnesses. Other authors, challenging the simplistic two-entity model, suggested the existence of a third entity or, alternatively, a spectrum model of psychosis with no point of rarity between the purely affective and the purely schizophrenic types. That position was supported when several symptom cluster analyses failed to reveal clear bimodal or trimodal aggregates of characteristics. Other authors persisted with the argument that schizoaffective disorder was really a misnomer and that patients so classified had been misdiagnosed. Throughout the 1970s opinion was divided on the issue, and the modest amount of empirical data was sufficiently contradictory that, when the third edition of DSM (DSM-III) was published in 1980, a category was inserted for schizoaffective disorder, but it was the only specific disorder for which no operationalized diagnostic criteria were included.

Research diagnostic criteria, DSM-III-R, and DSM-IV Reflecting additional research, the revised third edition of DSM (DSM-III-R), published in 1987, resolved DSM-III's ambiguity by adopting operationalized diagnostic criteria for schizoaffective disorder. Those criteria were descriptively similar to the Research Diagnostic Criteria (RDC), which had been in existence since the mid-1970s. In contrast to the RDC, though, DSM-III-R recognized the difficulty of making a purely cross-sectional diagnosis of schizoaffective disorder and incorporated certain longitudinal characteristics in the definition (for example, a requirement for at least two weeks of psychotic symptoms in the absence of major mood symptoms).

The bulk of the meaningful research currently available concerning schizoaffective disorder has used either the RDC or the DSM-III-R system of classification. The RDC further subdivides schizoaffective disorder into mostly affective and mostly schizophrenic on the basis of (1) core schizophrenic symptoms being present for at least one week in the absence of manic or depressive features and (2) features of deterioration—such as social withdrawal, impaired occupational functioning, eccentric behavior, and unusual thoughts or perceptual experiences—having occurred before the onset of the affective features. If either or both of those two characteristics are present, the patient is classified as mostly schizophrenic. The DSM-III-R criteria for schizoaffective disorder basically resemble the RDC criteria for the mostly schizophrenic subtype of schizoaffective disorder. Most patients meeting the RDC for the mostly affective type of schizoaffective disorder have been classified by DSM-III (or later by DSM-III-R) as having affective (or mood) disorders with mood-incongruent psychotic features.

DSM-IV retains the fundamental structure of the DSM-III-R diagnostic criteria for schizoaffective disorder but resolves some of the temporal ambiguities concerning the relationship of psychotic and mood symptoms. DSM-IV retains the DSM-III-R subdivision of schizoaffective disorder into a bipolar type and a depressive type on the basis of whether the patient has ever had a manic or mixed episode. That subdivision in DSM-III-R was originally based on the informative nature of the bipolar-unipolar distinction among patients with mood disorders. It has been continued in DSM-IV because empirical data have emerged that the distinction may correlate with certain family history, outcome, and treatment response data.

EPIDEMIOLOGY Changes in diagnostic standards over time have left studies of the epidemiology of schizoaffective disorder difficult to interpret. Depending on which of the various diagnostic criteria have been used, patients with schizoaffective disorder have been reported to constitute between 10 and 30 percent of psychiatric hospital admissions for functional psychosis. Studies have estimated the annual incidence of schizoaffective disorder to be 0.3 to 5.7 per 100,000 population and the lifetime prevalence of the disorder to be 0.5 to 0.8 percent. Those figures may be underestimates, however, inasmuch as one study (based on RDC criteria) that prospectively followed patients with an operationalized admission diagnosis of schizophrenia and rediagnosed them on a weekly basis found that in 20 percent of such patients the diagnosis was changed to schizoaffective disorder before discharge. Nevertheless, schizoaffective disorder is generally thought to be less common than schizophrenia.

The age at onset of schizoaffective disorder, as for schizophrenia, is typically late adolescence or early adulthood. No specific associations have been reported with sex, race, geographic area, or social class.

ETIOLOGY Psychological, psychodynamic, environmental, and interpersonal factors may play precipitating or triggering roles when they coincide with the biomedical diathesis that creates the vulnerability for decompensations of a schizoaffective nature. Little has been written concerning which psychological or interpersonal stresses are the most noxious to specifically schizoaffective persons, so hypotheses remain speculative in that regard. Issues considered to be important for patients with schizophrenia in particular and psychoses in general may well be applicable. Those issues include concerns regarding boundaries and difficulties in processing information overload because of a faulty stimulus barrier for external and internal stimuli. Similarly, themes known to be important in depression and mania, such as loss, loss of love, and internal standards, may also be important in schizoaffective disorder.

Proposed models of the diathesis Several hypotheses have been advanced concerning the nature of the underlying biological diathesis of schizoaffective disorder: (1) Schizoaffective disorder is a variant of schizophrenia. (2) It is a variant of a mood disorder. (3) It is a third psychosis, distinct from both schizophrenia and affective disorder. (4) Schizoaffective disorder is heterogeneous and consists of a subtype related to schizophrenia, a subtype related to a mood disorder, and perhaps a subtype that represents a third psychosis. (5) A unitary spectrum of functional psychosis extends from schizophrenia at one extreme to mood disorders at the other extreme, and schizoaffective disorder occupies an intermediate position on that spectrum. (6) Schizoaffective disorder is an interaction of schizophrenic and major mood disorder diatheses (a shared-diathesis model). Because no tissue diagnosis exists for either schizophrenia or mood disorders, those six hypotheses remain speculative, and the data relevant to them must be regarded

inferentially. The evidence has also tended to vary, not unexpectedly, with the definition of schizoaffective disorder used.

The family study and outcome data associated with the DSM-III-R definition of schizoaffective disorder, especially the depressive subtype, have often tended to suggest a relation to schizophrenia. That has also been the case for the RDC definition of the mostly schizophrenic schizoaffective disorder. For example, studies using each of those definitions have found that the relatives of schizoaffective patients have a rate of schizophrenia similar to the rate occurring in relatives of schizophrenic patients. Similarly, a twin-pair study found schizoaffective disorder to assort with schizophrenia, not with mood disorders. Studies using the cross-sectional RDC definition of schizoaffective disorder in general or the RDC mostly affective type in particular have tended to find a closer familial association of schizoaffective disorder with mood disorders than did studies that used DSM-III-R criteria. Earlier studies involving schizoaffective disorder patients with good outcomes had led to similar results, as did a more recent study involving schizomanic patients. Still other studies have provided evidence that atypical psychoses breed true—that is, although schizophrenic patients tend to have schizophrenic relatives and mood disorder patients tend to have relatives with mood disorder, schizoaffective patients were found to have relatives with schizoaffective disorder and *not* either schizophrenia or mood disorder. Those results support the third-psychosis hypothesis; however, the findings have not always been replicated. Several studies have found schizoaffective patients to have more relatives with mood disorder than do schizophrenic patients or controls, but fewer relatives with mood disorder than do patients with primary mood disorder. Analogous intermediate results were also found regarding schizophrenic relatives for those patients. Those results support the spectrum hypothesis, the heterogeneity hypothesis, or the diathesis interaction hypothesis.

The heterogeneity hypothesis has been supported by an argument that, although at least some data support each of the other hypotheses, other data argue against each of the other hypotheses, and no data clearly contradict the heterogeneity hypothesis. That argument, however, is weakened by the fact that it is hard to contradict a heterogeneity hypothesis—that is, many different findings can be considered to be part of the heterogeneity. Furthermore, almost all the genetic and family data can also be interpreted as consistent with a shared diathesis hypothesis.

Shared diathesis model The shared diathesis hypothesis is based on the assumption, supported by neuropsychiatric data, that the diathesis for schizophrenia is itself a continuum or a spectrum. A small number of patients have a high loading for the biological diathesis of schizophrenia, and presumably they will go on to develop schizophrenia, no matter what else occurs. A much larger number of persons have progressively smaller loadings with the schizophrenia diathesis. That relation is depicted by the curve in Figure 15.1-1. Toward the extreme left on the figure are those few persons who have such a massive biological loading for the perceptual and cognitive dysfunctions of schizophrenia that they are destined to develop that disorder virtually independently of any other circumstances they encounter. Toward the right side of the figure are the many persons with such a small loading for schizophrenia that they will probably never manifest any symptoms resembling the disorder. However, in the intermediate region are a substantial number of persons with some loading but not enough to make the occurrence of the disorder inevitable. For those people, psychotic symptoms reflecting their schizophrenic diathesis become manifest in the presence of additional biopsychosocial insults of sufficient magnitude. For patients who come to manifest schizophrenia (or, in milder cases, schizophreniform disorder), those insults may result from early brain injury (obstetrical complications); early viral infection (consistent with season of birth findings); early poor nutrition, psychological traumas, and social deprivations (all associated with poverty); substance abuse; or major psychological or social stresses at the time of the onset of the episode (the stress-diathesis model). Similarly, according to the shared diathesis model, an episode of a major mood disorder may constitute a sufficient stressor to activate (or, in combination with other insults, help activate) the underlying psychotic diathesis.

Such a model explains the close proximity of most psychotic symptoms to episodes of mood dysregulation in schizoaffective patients yet does not require the full diathesis of schizophrenia to be present in schizoaffective patients. Lack of requirement for a full diathesis in this situation is consistent with schizoaffective patients' more favorable premorbid course and outcome than schizophrenic patients. It is also congruent with the larger number of schizoaffective patients identified clinically than would be predicted on the basis of a requirement for a full schizophrenia diathesis coinciding with a full mood disorder diathesis. Therefore, the shared-diathesis model, although speculative, appears to be consistent with available family and genetic findings.

DIAGNOSIS AND CLINICAL FEATURES Considerable variability is possible in the presenting symptoms of schizoaffective disorder. All or any of the psychotic symptoms commonly associated with schizophrenia may be present during an acute episode. Those symptoms include delusions of various sorts, hallucinations, and evidence of thinking disturbances. The delusions are often paranoid in nature, although any kind of delusion is possible, including delusions of thought insertion or

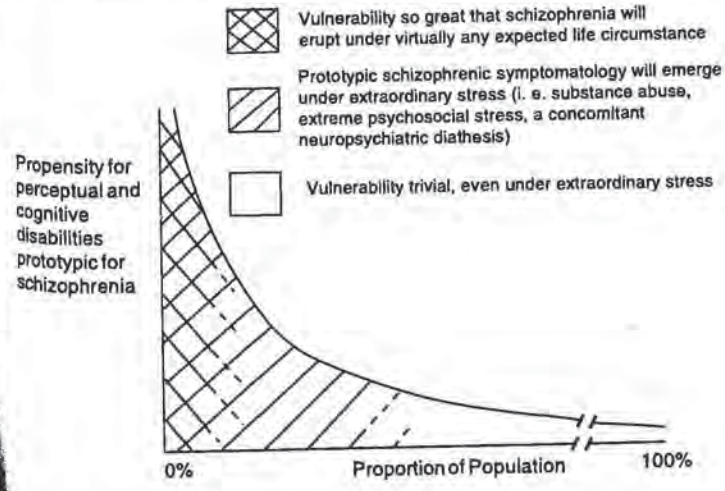

FIGURE 15.1-1 *Vulnerability to schizophrenic psychosis and its interaction with other stress factors.*

withdrawal, delusions of control, and fantastic or bizarre delusions. In addition, the delusions may be either congruent or incongruent with the patient's prevailing mood state. In the realm of perceptual aberrations, auditory hallucinations are the most common, followed in order by visual, tactile, olfactory, and gustatory hallucinations. Illusions or other perceptual distortions are also possible. Many of the disturbances of thinking in patients with schizoaffective disorder are also similar to those of schizophrenic patients. Although schizoaffective manic patients, like manic patients, have been noted to produce a substantial number of responses, the productions of schizoaffective patients often lack the humor or playfulness of those of manic patients. Schizoaffective patients also tend to generate a high percentage of idiosyncratic verbalizations, autistic thinking, and confusion. Schizoaffective depressed patients have also been noted to produce idiosyncratic and absurd responses on occasion.

Prominent mood disorder symptoms are also present in schizoaffective disorder. The symptoms may be of either the manic or the depressive variety (or both) and reach full and sustained syndromal proportions. Manic episodes include a distinct period of consistently elevated or irritable mood, with such associated features as grandiosity, a decreased need for sleep, overtalkativeness, racing thoughts, distractibility, increased activity or agitation, and a tendency toward excess without proper regard for the consequences. Patients in that manic state generally have a driven or excited quality. When they are in the throes of a manic episode, their behavioral aberrations are often fully ego-syntonic, doubt is absent, and they may exhibit an impenetrable sense of self-righteousness. Depressive episodes, however, are dominated by a blue mood, with such accompanying features as sleep or appetite disturbances; diminished level of interest or pleasure in usual activities; psychomotor retardation or agitation; subjective sense of energy loss; excessive or inappropriate guilt; feelings of worthlessness; diminished ability to think, concentrate, or make decisions; and recurrent thoughts of death or suicide. Depressive patients often feel hopeless and helpless, and their minds tend to be filled with the most negative images of themselves and upsetting, pessimistic, or otherwise gloomy thoughts. Although not all the characteristics of mania or depression are present in all patients, the clear gestalt is present and overlaps significantly with the time during which the patient is flagrantly psychotic. The psychotic and mood disorder symptoms are also of sufficient magnitude to impair social, occupational, and self-care functioning.

Also central to the concept of schizoaffective disorder is the episodic nature of the disturbance. Intervals of intensive illness tend to punctuate quiescent periods during which psychosocial functioning is adequate. Several researchers have emphasized the importance of that course-related characteristic in defining schizoaffective disorder, despite the convenience of ignoring that issue and making a symptom-based cross-sectional diagnosis at the time of a specific episode.

Pathology and laboratory examination Specific morphological, physiological, neuropsychological, and biochemical studies have usually not been undertaken in schizoaffective disorder. That lack is probably due to diagnostic inconsistencies and disagreements over the years and to the general assumption that the wisest course is to characterize such issues first in the well-defined pure mood disorders and schizophrenia. Nevertheless, a number of biological studies of schizophrenia have included patients with the RDC mostly schizophrenic type of schizoaffective disorder, because internal data analyses have failed to distinguish them from the larger group of schizophrenic patients studied.

Several neuroendocrine studies of schizoaffective disorder have been undertaken, and they have tended to show that the depressed type of schizoaffective disorder assorts with schizophrenia in terms of those parameters. Specifically, the rate of nonsuppression on the dexamethasone suppression test (DST) has been reported to be as low in patients with schizoaffective depression as it is in patients with schizophrenia or in normal control subjects and distinguishable from the higher rate noted in major depressive disorder. Similarly, the response of thyroid-stimulating hormone (TSH) and prolactin to an infusion of thyrotropin-releasing hormone (TRH) in schizoaffective patients has been observed to be similar to the response in schizophrenic patients and normal controls and not blunted, as is the case in many patients with major depressive episodes. Nevertheless, those schizoaffective patients who do have neuroendocrine responses paralleling endogenous depression are more likely to fully recover than are other schizoaffective patients. That observation appears to be independent of any family loading for mood disorders. Few studies have been undertaken in schizoaffective manic patients, though, and at least one of those studies presented results suggesting that the results of DST and TRH tests more closely approximate the results seen in patients with mood disorders than in nonmanic schizoaffective disorder patients. One study also found schizoaffective patients to resemble patients with bipolar disorder, rather than schizophrenic patients, in their rate of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) excretion.

DIFFERENTIAL DIAGNOSIS Schizoaffective disorder must be differentiated from mood disorders, schizophrenia, and other psychotic states with which it could be confused diagnostically.

Mood disorders Mood disorders that need to be differentiated include mania and psychotic depression. Manic patients can be flagrantly psychotic on occasion, manifesting hallucinations, delusions, and thought disorders, along with their full manic syndromes; thus, they resemble schizoaffective manic patients. The difference is that patients with pure mania do not have extended intervals (two weeks or more) during which hallucinations or delusions persist in the absence of prominent mood disorder symptoms. Similarly, although psychotic depressed patients may manifest either mood-congruent or mood-incongruent delusions and hallucinations, those features do not continue for as much as two weeks at a stretch in the absence of prominent mood disorder symptoms, as they do in schizoaffective disorder. In the midst of an episode, therefore, the diagnosis may not be clear, so the definitive assessment should be reserved for a time when the episode has concluded.

Schizophrenia One key to the differential diagnosis of schizoaffective disorder from schizophrenia is that a full affective syndrome—mania or depression—must be present in schizoaffective disorder. Mood symptoms of various types may be present or even prominent in the course of an episode of schizophrenia, but, in the absence of a full and sustained mood syndrome, the diagnosis of schizoaffective disorder should not be made. The appropriate diagnosis is schizophrenia, not schizoaffective disorder, even when a full mood syndrome is present, if all the episodes of mood disturbance are brief in comparison with the full duration of the psychotic episode. In addition, the appropriate diagnosis is schizophrenia if the full mood syndrome occurs only during the residual phase of schizophrenia and not during the course of the flagrant psychotic episode.

That last circumstance is the one that applies in the diagnosis of the syndrome of postpsychotic depression in schizophrenia. Postpsychotic depression is diagnosed when the full depressive syndrome occurs in schizophrenic patients who are either nonpsychotic or only residually psychotic. The syndrome may occur either soon after the resolution of a psychotic episode or substantially later; and it has been estimated to occur in about 25 percent of schizophrenic patients. Postpsychotic depression has been reported to respond to the gradual introduction of antidepressant medication, in addition to an ongoing antipsychotic-antiparkinsonian regimen, whereas an adjunctive antidepressant

may not be indicated in acute episodes of schizoaffective depression.

Akinesia Schizoaffective depression (or postpsychotic depression, depending on the temporal sequence involved) must also be differentiated from the neuroleptic-induced extrapyramidal side effects of akinesia. The akinesia syndrome may manifest with a lack of spontaneity (impairment in the initiation or the sustaining of behaviors), even in the absence of other obvious motor side effects, such as stiffness, cogwheeling, or reductions in accessory motor movements. The presentation of akinesia can easily be confused with the lack of energy or the anhedonia of depression. Furthermore, patients with neuroleptic-induced akinesia sometimes manifest a sad mood and experience guilt or self-blame for their condition—features that can accentuate the degree to which their state resembles a form of depression. Fortunately, neuroleptic-induced akinesia is often quickly responsive (that is, within several days) to full dosages of anticholinergic antiparkinsonian medications, and a trial of those compounds is often the most effective way to make the diagnosis.

The negative symptoms of schizophrenia can easily be confused with depression or akinesia. Anhedonia and anergia are often prominent and central components of the negative symptom syndrome, and they can be clear phenocopies of the anhedonic and anergic states that are common in depression. Blue mood, however, is not a component feature of the negative symptom syndrome. In fact, some have described flat affect as the central aspect of negative symptoms.

Akathisia Akathisia is another neuroleptic-induced side effect that can mimic mood disorder symptoms. The motor restlessness of severe akathisia can resemble mania in the way the patient stays in almost constant motion. In akathisia, however, the patient experiences the state of constant activity as uncomfortable or unpleasant. The patient wishes to stop or rest but feels unable to do so. In mania, by contrast, the patient feels that the motor activity, however excessive, is something originating in the patient's own initiative and is behavior the patient wishes to engage in. Neuroleptic-induced akathisia may also resemble the agitation that is sometimes a component of the depressive syndrome. Because akathisia is unpleasant, often markedly so, the associated dysphoria can be mistaken for depression. Suicidal impulses have been described in states of akathisia and can mimic depression. Obviously, increasing the dosage of neuroleptics only makes akathisia worse. Decreasing the neuroleptic dosage, if possible, is the best treatment, and a positive response to that intervention helps make the diagnosis. Benzodiazepines and propranolol (Inderal) are the adjunctive medications most often effective in controlling neuroleptic-induced akathisia.

Substance abuse Substance abuse, both acute intoxication and chronic states, can result in clinical presentations indistinguishable in cross section from schizoaffective disorder. Psychostimulants can initially generate excited psychotic states resembling schizoaffective mania, but the crash that may follow can also resemble the depressed form of schizoaffective disorder if psychotic features persist into that interval. The amotivational syndrome associated with chronic cannabis use can easily be mistaken for depression. Use of psychotomimetics, other street substances, and even alcohol can cause mixed psychotic and mood states in various stages of intoxication or withdrawal. That is true for patients in whom substance abuse occurs alone and for patients with either pure schizophrenia or a pure mood disorder who may appear schizoaffective under the influence of various substances. A screen for substances of abuse is indicated with any patient in whom the diagnosis of schizoaffective disorder is being considered.

Medical illnesses A variety of medical illnesses can lead to mixed states of mood and psychotic symptoms. A proper medical workup therefore needs to be performed to rule out the possibility of a medical illness.

COURSE AND PROGNOSIS

The course and the outcome of schizoaffective disorder, on the whole, tend to be more favorable than the course and the outcome of schizophrenia but less favorable than those of a pure mood disorder. Bipolar schizoaffective patients who also have histories of pure mood disorder episodes have been reported to have outcomes no less favorable than patients with major mood disorders, although other patients with schizoaffective mania have been noted to manifest more psychotic symptoms, more subsequent maniclike episodes, and poorer social outcomes than do pure manic patients.

Patients with a number of schizoaffective depressive episodes and those who have histories of both schizoaffective depressed and schizophrenic episodes tend to have significantly poorer outcomes than patients who do not. Studies have also found that, when a full schizophrenic syndrome is present in schizoaffective disorder patients, along with the mood syndrome (only a full affective syndrome is required for the diagnosis of schizoaffective disorder, not a full schizophrenic syndrome), poorer outcomes occur than in schizoaffective disorder patients without a full schizophrenic syndrome. Overall, a substantial degree of outcome heterogeneity is found in general, and notable inconsistencies are seen within and between patients in terms of social, vocational, and symptomatic domains of outcome.

TREATMENT

Schizoaffective mania

ACUTE TREATMENT Antipsychotics and lithium are the psychopharmacological agents most often used in the treatment of schizoaffective mania, and both have value in controlling the acute symptoms. In the studies that have made the comparison, associations have usually not been found between the most prominent symptoms and the specific degree of usefulness of one or the other of those two agents within the diagnostic category. An important distinction was found in one large collaborative study, however, when patients were subdivided on the basis of level of activation. In that study, highly active patients were found to benefit more from treatment with the antipsychotic agent—in that case, chlorpromazine (Thorazine)—than from lithium, and the two drugs were found to have equivalent efficacy among moderately active patients. Low-potency antipsychotic compounds have the side effect of sedation, which can be clinically useful in controlling excited patients. Other side effects, such as constipation, dry mouth, blurred vision, and orthostatic hypotension, also accompany the use of low-potency antipsychotic agents. As always, clinical judgment is required to balance the medication effects and side effects that best match the patient's psychiatric and medical status.

Certain studies have suggested that the combination of lithium and an antipsychotic may be more effective than the use of either agent alone. Although the side effects are increased by combined treatment, the best evidence is that the effects are merely additive. Reports indicate that the benefit of adding lithium to antipsychotics in the treatment of schizoaffective manic patients extends throughout the entire range of the patients' symptoms and is not restricted to the mood component. In all cases of the use of antipsychotics or lithium or their combination, the standard dosages recommended for their use in schizophrenia and

mania are recommended, and monitoring of blood lithium levels is required. An episode of schizoaffective mania, however, can be expected to resolve more slowly than an episode of mania, and the resolution may be less complete in schizoaffective mania than in mania.

Electroconvulsive therapy (ECT) can also be an effective acute treatment of schizoaffective mania, and its use should be considered when the most rapid possible response is important (for example, in dangerous situations) and when the patient appears to be refractory to other interventions. Carbamazepine (Tegretol) and valproic acid (Depakene) are alternative adjunctive medications that may be effective when added to the antipsychotic or to lithium (or both) in difficult cases.

CONTINUATION AND MAINTENANCE TREATMENT Lithium is effective in the prophylactic management of schizoaffective mania or the bipolar type of schizoaffective disorder when it is used at plasma levels of 0.60 mEq/L or above. It is most useful in patients with the most severe affective symptoms. As is the case with other patients receiving long-term lithium treatment, consistency of fluid and sodium intake and routine surveillance of lithium levels and kidney and thyroid function are indicated. Patients, their families, and other caretakers should be informed about the early signs of lithium toxicity and what to do should the signs occur.

Because tardive dyskinesia is a risk with long-term antipsychotic treatment, perhaps especially in patients with mood disorder features, it is reasonable to discontinue antipsychotic medications and attempt a long-term treatment trial of lithium alone for schizoaffective mania. However, lithium by itself may not prove adequate. In that case, antipsychotics should be titrated down to the lowest dosages that provide suitable protection. Indeed, small antipsychotic dosages may allow for the optimal level of psychosocial functioning while slowing the progression of new episodes, even if the antipsychotics do not abort the episodes entirely. A strategy of intermittent antipsychotic dosing may be appropriate for patients who themselves or in conjunction with their support systems are able to detect impending episodes and instigate treatment.

Schizoaffective depression

ACUTE TREATMENT Although the combination of an antipsychotic and an antidepressant may be a good choice of treatment in psychotic depressions, support for such a strategy is much more meager in schizoaffective depression. One controlled study did show an advantage for that combination over either component given alone, but the most recent, carefully controlled, prospective study indicated that the addition of an antidepressant to the antipsychotic actually slowed the improvements of acutely psychotic schizoaffective depressed patients. Lithium also does not have a high likelihood of being helpful for schizoaffective depressions, especially in patients who do not have a history of bipolar disorder-type mood changes. Therefore, the best initial approach to a psychotic patient with the diagnosis of schizoaffective depression is likely to be treatment with a simple antipsychotic-antiparkinsonian combination, with a dosage strategy similar to that used for schizophrenia. In many cases the symptoms of depression disappear coincident with the fading of the psychotic symptoms. If the psychotic symptoms resolve but the depressive symptoms remain, the first course of action should be to rule out the possibility of neuroleptic-induced akinesia with antipsychotic dosage reduction (if feasible). Alternatively or in conjunction, a vigorous trial of antiparkinsonian medication may be undertaken. If a syndrome of depression persists in a consistent fashion, a trial of an antidepressant medication, gradually increasing to the full dosage used in primary depression, added to the antipsychotic-antiparkinsonian combination is appropriate. The patients, therefore, are treated much the same as patients meeting the DSM-IV criteria for postpsychotic depression.

ECT is also worth considering in schizoaffective depression. Although empirical studies with modern diagnostic criteria are lacking, a trial of ECT is appropriate in refractory cases.

CONTINUATION AND MAINTENANCE TREATMENT The best course of treatment is probably to continue whatever treatment was useful in leading to the remission of an acute episode. As noted earlier, lithium is less likely to be effective in schizoaffective depression than in schizoaffective mania. The same cautions referred to earlier regarding the use of antipsychotics and other agents for the long-term treatment of schizoaffective mania also apply to schizoaffective depression.

Adjunctive medications Antiparkinsonian medications are indicated when antipsychotic medications are used for the treatment of acute schizoaffective episodes. That precaution helps avert acute dystonias and other acute and unpleasant extrapyramidal side effects that may be associated with antipsychotics. That action is also helpful in avoiding lack of compliance with antipsychotic regimens (or with treatment altogether) because of how unpleasant the side effects can be. Even in continuation and maintenance phases, adjunctive antiparkinsonian agents may be essential for the same reasons. And in the later stages of treatment, adjunctive antiparkinsonian drugs may be crucial to prevent neuroleptic-induced akinesia, which can at times closely resemble negative symptoms or depression.

Benzodiazepines may be valuable adjuncts for the treatment of anxiety or insomnia during acute schizoaffective episodes. In that role they may also contribute to the antipsychotic effects or allow for a lower dosage of antipsychotic medication than might otherwise be possible. Benzodiazepines can also be useful in the treatment of neuroleptic-induced akathisia, should that occur, although other medications, such as propranolol, may also be useful in that situation. During maintenance treatment, an adjunctive benzodiazepine or propranolol may be indicated for similar reasons.

During the maintenance phase, adjunctive antidepressants may be useful in the treatment of secondary depressive episodes that emerge in patients with schizoaffective disorder during intervals in which they are not flagrantly psychotic. After the confounding syndrome of neuroleptic-induced akinesia is ruled out, the treatment of such a depressive episode is similar to the treatment of postpsychotic depression in schizophrenia, with the gradual addition of full dosages of antidepressant medications to an ongoing antipsychotic-antiparkinsonian regimen.

Psychosocial interventions Although somatic treatments directly address the biological diatheses that are involved in schizoaffective disorder, prominent morbidities occur in the course of the illness that are fundamentally psychological or social. Those morbidities need to be addressed with appropriate interpersonal modalities to help patients and their familial, social, and vocational support networks cope with the onslaught of acute episodes and the recuperative and reconstructive tasks involved during the postacute phases of treatment. Psychodynamic issues deserve careful attention, inasmuch as intrapsychic conflicts can be important triggers or perpetuators of psychotic symptoms in accordance with the stress-diathesis concept. Supportive interventions are indicated, but uncovering or exploratory techniques are generally to be avoided, especially during the acute stages of illness. Psychotic patients often have trouble

organizing the turmoil generated by the uncovering of powerful primitive instinctual drives that are ordinarily held outside the domain of conscious awareness. Instead, structured, integrated, and problem-solving psychotherapeutic interventions should be used, although the therapist should remain alert to and respectful of important psychodynamic issues.

Psychiatric hospitalization is often required at the time of acute psychotic episodes since the patients' loss of reality testing, judgment, and thinking ability and the overwhelming press of their affectivity may have outstripped their (and their support networks') ability to attend to their immediate needs. A hospital provides 24-hour structure and guidance designed to protect patients from their own impulses and lack of judgment, which otherwise may result in harm to themselves or others, whether that harm is physical (suicide, assaultiveness), financial, legal, vocational, or social. A hospital also provides protection or, quite literally, asylum from outside stressors that may be triggering or exacerbating the patients' conditions.

During hospitalization, coincident with somatic treatments, an evaluation of the patient's life situation and coping capacities takes place, and interventions are instituted to reinforce the most constructive aspects of those capacities to allow the reinstitution of appropriate autonomies. Simultaneously, the patient's psychosocial support network is examined, both to enhance the treatment team's understanding of the tasks with which the patient has to cope and to interact with that network, when possible, to allow the network to provide a good fit with the patient's adaptive needs through such interventions as psychoeducation, the reduction of expressed emotion, and the provision of concrete social services.

Hospitalization should not be continued longer than required so as not to foster unnecessary regression and dependence. Step-down levels of care, such as partial hospitalization, continued day treatment, or halfway houses, can be valuable psychosocial supports and can provide patients with a more normative environment than a hospital and the opportunity to resume responsibilities for which they have regained capability. In those environments and in the clinic environments to which patients may then progress, suitable programs of rehabilitation should be provided for building and practicing social and vocational skills that they either previously lacked or did not fully regain after the resolution of the acute episode. In those programs, respect for and attention to the patients' natural skills, interests, and aspirations become as important as the recognition of their problems and deficits.

A 25-year-old male teacher directing a high school play involving a murder became convinced that the murder in the play reflected a real one. He also believed that he was in danger from the unknown perpetrator and several cast members. That state persisted for three weeks, during which time he gradually stopped talking to his associates. His need for sleep diminished, and he started wandering the streets at night, searching for clues. He became increasingly excited as he concluded that an international intrigue underlay the murder he was solving. At that point he felt the "pressure of world history," and his behavior became frenzied. His speech was accelerated, he had the subjective sense that his thoughts were racing with great clarity, and he got into heated and irrational arguments with other teachers who offered to help with the play. When he finally confided to his girlfriend that his directing the play to a surprise ending would result in the release of Middle Eastern hostages, she arranged for his hospitalization.

On admission to the hospital, his physical examination and laboratory results were normal, and a substance abuse screen was negative. After three weeks of chlorpromazine treatment, the patient's sleep pattern normalized. He appeared to be relaxed, and he began conversing with staff members. He continued to suspect that the play had a hidden meaning but acknowledged that it did not have international implications. Lithium was added to his regimen, and after two more weeks he was discharged. As an outpatient, he continued to do well as the chlorpromazine was gradually tapered, and he successfully returned to his teaching.

Three years later, after stopping the lithium medication on his own, the patient suffered a similar psychotic decompensation. Hospitalized, he again responded to an antipsychotic plus lithium. Subsequently, he has continued to take lithium for six years without further episodes. He has continued to teach and has several good friends. However, he has lost interest in theater activities and remains unmarried.

SCHIZOPHRENIFORM DISORDER

Schizophreniform disorder was first described in relatively broad terms in patients with abrupt onsets of psychotic illness and favorable prognoses, but it has since been redefined to include a more restricted group of patients. The impetus for the diagnostic term stemmed from the observation that some patients diagnosed as having schizophrenia did not progress to a chronic disorder or display deterioration in functioning. The term allows the clinician to guard against the premature diagnosis of schizophrenia and may help the patient avoid unnecessary treatment and stigma. Studies assessing the validity of the contemporary definition of schizophreniform disorder have yielded conflicting results, and additional studies and experience are needed to establish the disorder's existence, boundaries, and characteristics.

DEFINITION DSM-IV defines schizophreniform disorder as identical to schizophrenia with the prime exceptions of duration of illness and the requirement for a deterioration in social or occupational functioning (Table 15.1-2). During the acute episode, psychotic symptoms—including delusions, hallucinations, disorganized thinking, and catatonic behavior—may all be present, as in schizophrenia, but the total episode of disturbance—including prodromal, active, and residual phases—is defined as between one and six months' duration. When the diagnosis of schizophreniform disorder must be made without waiting for recovery, it should be qualified as provisional. If symptoms then persist for longer than six months, subchronic schizophrenia becomes the accurate diagnosis. Although many patients experience dysfunction in various areas of daily living, impairment in social or occupational functioning is not required to diagnose schizophreniform disorder. Schizophreniform disorder is not to be diagnosed if the disturbance is substance-induced or due to a general medical condition or if the disorder, including the prodromal and residual phases, lasts less than one month. Patients may be further classified as having good prognostic features or not.

HISTORY Gabriel Langfeldt first coined the term "schizophreniform disorder" in 1939 to classify a group of psychotic patients with

TABLE 15.1-2
Diagnostic Criteria for Schizophreniform Disorder

A. Criteria A, D, and E of schizophrenia are met.
B. An episode of the disorder (including prodromal, active, and residual phases) lasts at least one month but less than six months. (When the diagnosis must be made without waiting for recovery, it should be qualified as "provisional.")

Specify if:
Without good prognostic features
With good prognostic features: as evidenced by two (or more) of the following:
(1) onset of prominent psychotic symptoms within four weeks of the first noticeable change in usual behavior or functioning
(2) confusion or perplexity at the height of the psychotic episode
(3) good premorbid social and occupational functioning
(4) absence of blunted or flat affect

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

good prognoses. It represented an attempt to classify patients who had been described as schizophrenic but who did not display deterioration in overall functioning. They had, for example, acute reactions that were often precipitated by stress. Many of the patients exhibited good premorbid functioning, depressive or hysterical features, and clouding of consciousness during the acute psychosis. The original concept of schizophreniform disorder included several other conditions, and Langfeldt wrote that both schizoaffective disorder and brief reactive psychosis should be included under the term. His intention was to differentiate patients with "genuine schizophrenia" from others who did not experience a poor outcome and a declining course.

Subsequent investigators continued to use the term "schizophreniform disorder" for a number of conditions, including schizoaffective disorder. With the introduction of DSM-III, however, the original concept of schizophreniform disorder was altered. Since then, the term has been used for a condition considered identical to schizophrenia except for its duration.

COMPARATIVE NOSOLOGY Schizophreniform disorder was not included in DSM-I or DSM-II. DSM-II defined a heterogeneous condition, acute schizophrenic episode, that included acute schizophrenic symptoms accompanied by confusion, emotional turmoil, excitement, and depression in some cases. Some patients were noted to recover within weeks, but others progressed much more slowly. The eighth and ninth revisions of the *International Classification of Diseases and Related Health Problems* (ICD-8 and ICD-9) did not use the term "schizophreniform disorder." "Schizophreniform" appeared in the glossary of ICD-9 but was not defined.

In 1980 DSM-III defined schizophreniform disorder in much the same terms as schizophrenia except that the total duration of symptoms was limited to six months. It also excluded patients with mood disorder and brief reactive psychosis. In 1987 DSM-III-R sought to define schizophreniform disorder more carefully than in the past by including the term "provisional" so that the clinician could make the diagnosis before waiting for the six-month period to elapse. It also allowed for the specification of with and without good prognostic features, with at least two of four features required to define good prognosis. Those features, however, had been the subject of few studies and appeared to be relatively nonspecific in terms of outcome. Differentiating schizophreniform disorder of less than one month's duration from brief reactive psychosis in DSM-III and DSM-III-R also proved to be difficult. DSM-IV has set a one-month requirement for active symptoms to appear after the first noticeable change in behavior or functioning.

EPIDEMIOLOGY Few studies have examined the incidence or the distribution of schizophreniform disorder as defined by DSM-III, DSM-III-R, or DSM-IV. True schizophreniform disorder seems to be a rare condition, and in many studies more than half of the patients are reclassified at follow-up as suffering from schizophrenia. One large review suggested that a small subgroup of patients (0 to 29 percent) exhibit a remitting nonaffective psychosis. Community studies have reported a lifetime prevalence of schizophreniform disorder of approximately 0.2 percent and a one-year prevalence of 0.1 percent. The age at onset of schizophreniform disorder is believed to be similar to that found in schizophrenia—primarily adolescence and early adulthood. Little information is available concerning sex, race, or social class distribution. Family studies have used small numbers of patients, differing definitions of schizophreniform disorder, and mostly retrospective reviews. Their conflicting data have left it unclear whether the relatives of patients with schizophreniform disorder have an increased risk of schizophrenia, although some evidence supports an increased risk of psychotic mood disorders among the relatives. Although the rate of schizophreniform disorder has been observed to be less than 5 percent of all patients with a first episode of psychosis, the rate may be higher in developing countries, where recovery from psychotic episodes may be more rapid than in developed countries.

ETIOLOGY The cause of schizophreniform disorder is unknown. A number of hypotheses have been generated for schizophrenia and mood disorders, but it is unclear whether similar theories of cause or pathophysiology should be applied to schizophreniform disorder. Of the existing hypotheses concerning the pathophysiological mechanism of schizophreniform disorder, dopamine receptor supersensitivity is probably the leading candidate.

Because existing family studies are limited by methodological flaws, it is also unknown whether there is a genetic predisposition for the development of schizophreniform disorder. In general, the relatives of patients with schizophreniform disorder do not seem to share an identical pattern of psychiatric illness when compared with the relatives of patients with schizophrenia. Much of the early literature suggested a familial link with mood disorders, and, since the publication of DSM-III, the majority of family studies of patients with schizophreniform disorder favor the idea that their relatives are at increased risk for mood disorders. A couple of those studies also concluded that relatives of probands with schizophreniform disorder have an intermediate risk for schizophrenia when compared with the relatives of patients with schizophrenia (who had the greatest risk) and mood disorders.

Biological and laboratory markers validating the presence of schizophreniform disorder and distinguishing it from other forms of psychiatric illness have not appeared. In several studies, computed tomography (CT) scans failed to detect significant differences between patients with schizophreniform disorder and those with schizophrenia, although both types of patients displayed increased ventricular brain ratios when compared with controls or patients with other types of psychiatric illness, including mood disorders. However, in a study of neuroendocrine markers, patients with schizophreniform disorder exhibited abnormal dexamethasone suppression at a rate intermediate between the rate of those with schizophrenia and those with mood disorders and a frequency of blunted TSH response to TRH that was similar to that of patients with mood disorders and greater than that of schizophrenic patients. In another study involving growth hormone (GH) response to apomorphine, patients with schizophreniform disorder had larger GH responses than did schizophrenic patients, again suggesting biological dissimilarities. A study of abnormalities of smooth-pursuit eye movements found that schizophreniform patients and their relatives had similarly low rates of abnormalities as compared with normal control subjects and a schizophrenic control group. In another study, a battery of neuropsychological tests revealed that schizophreniform patients performed significantly worse than normal subjects but had similar cognitive deficits as patients with chronic schizophrenia.

Although many patients with schizophreniform disorder experience significant psychological or social stressors before the onset of their disorders, the role of specific psychosocial stressors has not been carefully evaluated in controlled studies of those patients. Psychodynamic and other psychological or social factors presumably can function as triggers of psychotic episodes in accordance with the stress-diathesis model.

DIAGNOSTIC AND CLINICAL FEATURES Patients with schizophreniform disorder often appear in a floridly psychotic state, with a relatively abrupt onset of auditory or visual hallucinations, delusional thinking, and bizarre behavior. That state may manifest in an agitated or threatening manner or as a withdrawn or catatonic condition. In the short term, patients with schizophreniform disorder do not differ from schizophrenic patients in their manifest psychopathology or severity of symptoms. Acute affective symptoms may be present, but a full affective syndrome is not sustained. By definition, the active phase of the illness persists for at least one month. At present, no specific imaging techniques or laboratory studies are able to distinguish schizophreniform disorder from other psychiatric illnesses.

The total duration of an episode of schizophreniform disorder—including prodromal, active, and residual phases—is at least one month but less than six months. Although the patients may have multiple episodes or hospitalizations, their social and occupational functioning is generally intact at other times, as the patients tend to recompensate well after the episode.

Several prognostic features have been proposed, although they have been the subject of few controlled studies. At least two of the following criteria allow for the specification of the good prognosis subtype in DSM-IV: (1) the onset of prominent psychotic symptoms within four weeks of the first noticeable change in the patient's usual behavior or functioning; (2) con-

fusion, disorientation, or perplexity at the height of the psychiatric episode; (3) good premorbid social and occupational functioning; and (4) the absence of blunted or flat affect. Many patients present with one or more of those features.

DIFFERENTIAL DIAGNOSIS Distinguishing schizophreniform disorder from other medical and psychiatric conditions that may present in a floridly psychotic state can be challenging. A detailed history should focus on the time of symptom onset, the course, the patient's premorbid functioning, the precipitants, the patient's physical health, the use of medications, the patient's use of alcohol and other substances, the family history, and the presence of any previous episodes. Such a detailed history may require the assistance of family members or others familiar with the patient. The often abrupt onset of symptoms, coupled with the lack of previous episodes in many cases, underscores the need for a toxicological and medical evaluation.

Substance abuse is one of the most common causes of the abrupt onset of psychotic symptoms, and a toxicology screen is indicated in any such case to aid in the diagnosis. A number of medical and neurological disorders may also manifest with symptoms characteristic of schizophreniform disorder. Those conditions include various metabolic and endocrine disorders, cerebral tumors, meningitis, and temporal lobe epilepsy. If the mental status examination reveals an absence of a clear sensorium or difficulty in maintaining attention, a general medical condition and delirium should be considered.

Dating the exact onset of such an illness can be difficult, and prodromal symptoms may be subtle. When symptoms clearly persist for more than six months, though, the diagnosis of another psychiatric disorder must be made. The possibilities include schizophrenia, schizoaffective disorder, a mood disorder with psychotic features, delusional disorder, substance-induced psychotic disorder, and psychotic disorder due to a general medical condition. An especially difficult distinction to make occurs in patients with affective symptoms in the setting of an acute psychosis. Insomnia, fatigue, irritability, and decreased concentration may be secondary events, for example, in a patient struggling with persistent auditory hallucinations. Although patients with schizophreniform disorder sometimes meet the criteria for mood disorders, the psychotic symptoms are the most prominent. When symptoms have been present for less than one month and there is a stressful precipitant, the diagnosis of brief psychotic disorder should preempt the diagnosis of schizophreniform disorder.

COURSE AND PROGNOSIS By definition, schizophreniform disorder is marked by a short course, with symptoms present from one to six months. Patients usually display good premorbid functioning, and at least a fourth recover fully, returning to their baseline social and vocational states on resolution of the psychotic episode. In general, although most outcome studies indicate that patients with schizophreniform disorder do significantly better than schizophrenic patients, they do not do as well longitudinally as patients with mood disorders. A significant number of patients relapse, and long-term follow-up studies suggest that more than half of patients with schizophreniform disorder are reclassified at a later time as having schizophrenia, schizoaffective disorder, or a mood disorder with psychotic features. As a group, patients with schizophreniform disorder have higher mortality and suicide rates than the general population.

DSM-III-R and DSM-IV specify several prognostic signs and symptoms in an effort to predict the course of the illness. The abrupt onset of symptoms, confusion or perplexity at the height of the psychotic episodes, a brief duration of illness at index admission, good premorbid social and occupational functioning, and the absence of blunted or flat affect are all thought to be favorable prognostic signs.

Few available biological indicators suggest whether an acute first-episode psychosis will become chronic, although neuroendocrine dysfunction may provide some prognostic information. One study found that a high percentage of patients with schizophreniform disorder in whom symptoms remitted had an abnormal DST or TRH-stimulating test. However, that finding may have been confounded by underlying mood disorders in some of the patients studied.

The patient's response to antipsychotic medication may also prove useful in determining the course of the disorder. A recent limited study showed that patients with schizophreniform disorder responded faster than schizophrenic patients to antipsychotic medication. Further, those with a delayed response seemed to have a longer illness course than did rapid responders.

TREATMENT No controlled studies of the treatment of schizophreniform disorder are available to help guide clinicians. As a result, the prevailing approach to treatment for the acute psychotic condition comes from what is known about the short-term responses of schizophrenic patients. In general, the aims are to protect and stabilize the patient, minimize the psychosocial consequences, and resolve the target symptoms with minimal side effects. Another study suggested that left ventricular enlargement in patients with schizophreniform disorder correlated with progression to schizophrenia or schizoaffective disorder at a one-year follow-up.

The patient often needs hospitalization, which not only allows for complete diagnostic evaluation but helps ensure the safety of the patient, who may be at risk of harming himself or herself or others. A supportive environment with minimal stimulation is most helpful. As improvement progresses, help with coping skills, problem-solving techniques, and psychoeducational approaches may be added for patients and their families.

When patients are actively hallucinating and delusional, antipsychotic medications are the psychopharmacological agents of choice. If patients are extremely agitated, the intramuscular route of administration is preferred for prompt relief of symptoms. Prophylactic antiparkinsonism medication should also be offered to help reduce the likelihood of acute extrapyramidal symptoms. That medication not only helps improve compliance but may also help preserve the therapeutic alliance at that early stage of treatment. The adjunctive use of small dosages of benzodiazepines may also be beneficial at times of increased anxiety or agitation. If the patient or a family member has a history of response to treatment, that may prove to be a valuable guide. Other medications, such as lithium and antidepressants, may be indicated after further observation and the gathering of additional history.

At present, it is unclear how long patients should be maintained on medication after the resolution of their florid symptoms. The regimen needs to be based on characteristics of the individual case and consideration of medication side effects, such as tardive dyskinesia. By definition, schizophreniform disorder is limited in duration and should not require prophylactic antipsychotic medication. However, gradual tapering of medications is more likely to be a successful strategy than abrupt discontinuation. Further, patients need to be monitored during and after medication termination because a substantial proportion experience a recurrence of symptoms.

After the acute psychotic episode has resolved, psychosocial

interventions, including individual, group, and family therapy, may be useful. Supportive psychotherapy can be targeted to improve patients' self-esteem and restore their sense of autonomy. In general, clinicians should focus on problem-solving strategies, improving communication skills, and reducing stress. Doing so enables patients to cope in the world outside the hospital. Patients may benefit from a structured intermediate environment, such as a day hospital, during the initial phases of returning to the community. Involvement of the patients' external support systems in the treatment plan is also beneficial. Efforts should be made to educate both the patients and their families about the early signs of relapse and the need for continuing treatment. Those approaches advance the overall aim of helping patients regain productive roles in society while reducing the risk of relapse.

A 21-year-old single male college sophomore who had previously worked steadily and had a pilot's license was referred for psychiatric hospitalization after the onset of auditory hallucinations and paranoid thinking one month previously. He complained to his parents about neighbors calling him names for unknown reasons and about their children wanting to harm him. In addition, he claimed to hear criticizing voices in his head. He often stayed awake at night, pacing, and was unable to continue his studies, withdrawing into his room. He was aware of no clear precipitants other than feeling stressed by the recent sickness of his father. He had no previous psychiatric or medical history, and he denied any drug or alcohol use.

On admission to the hospital, the results of a laboratory workup, including CT of the brain and an electroencephalogram (EEG), were unremarkable. The results of the toxicology screen for substances of abuse were negative. The patient responded markedly within three weeks after starting to take an antipsychotic medication. He no longer noted any hallucinations and denied any paranoid ideation. He also seemed to benefit from a combination of individual, group, and family therapies. He continued taking the medication for six months after discharge from the hospital and was able to return to school and obtain his degree. At follow-up three years later, he remained symptom-free.

BRIEF PSYCHOTIC DISORDER

Brief psychotic disorder, a new diagnostic category in DSM-IV, incorporates brief reactive psychosis, the designation for a disorder that is clearly a response to markedly stressful events.

Brief psychotic disorder is one of the least understood and least investigated forms of functional psychosis. Although the diagnosis of brief psychotic disorder started to gain increased consideration by American psychiatrists, it has traditionally been the subject of study by Scandinavian researchers. As defined by DSM-IV, brief psychotic disorder includes active psychotic symptoms that persist for periods ranging from at least one day to one month. By definition, that period is followed by a full return to premorbid levels of functioning. The onset is often abrupt and, according to some, serves as a defense reaction to avoid the pain associated with a traumatic event. The illness has been called by various names over time and in different countries, and it remains a concept plagued by much confusion, with most studies hampered by unclear diagnostic criteria and other methodological flaws.

DEFINITION DSM-IV defines brief psychotic disorder as an illness lasting from one day to one month, with eventual return to premorbid levels of functioning. At least one of the following symptoms indicative of impaired reality testing is required: delusions, hallucinations, disorganized speech, catatonia, or grossly disorganized behavior. When symptoms occur after and in response to one or more events that, singularly or together, would be markedly stressful to almost anyone in similar circumstances in that person's culture, then the further designation of brief reactive psychosis is appropriate (called brief psychotic disorder with marked stressors in DSM-IV). The exclusion criteria include the presence of a full mood syndrome (mood disorder with psychotic features), schizoaffective disorder, and any substance-induced psychotic disorder or psychotic disorder due to a general medical condition. If the diagnosis must be made without waiting for the expected recovery, it should be qualified as provisional. The DSM-IV diagnostic criteria are listed in Table 15.1-3.

That definition modifies the DSM-III and DSM-III-R diagnostic criteria to make them less restrictive. Emotional turmoil or confusion is no longer necessary during the reaction. Cases in which a precipitating stressor is absent are included under the rubric brief psychotic disorder, but the specifier, without marked stressor, should be noted. An additional specifier, with postpartum onset, notes the onset of psychotic symptoms within four weeks postpartum.

HISTORY For well over a century, investigators have used various terms to define psychotic states that seem to occur in response to a stressful life event. Such terms have included hysterical psychosis, *bouffée délirante*, psychogenic psychosis, reactive schizophrenia, good-prognosis schizophrenia, cycloid psychosis, transient psychosis, and atypical psychosis. In nonindustrialized countries such terms as yak, latah, koro, amok, and whitigo psychosis have been used to describe psychotic states precipitated by stressful events.

In 1913 Karl Jaspers offered specific criteria for reactive psychosis. First, a precipitating factor should have occurred shortly before the onset of the reactive state. Second, it should be an adequate factor and should have a meaningful connection with the abnormal reaction. Third, the psychosis should remit when that factor is removed. Over time, the "understandability" of the symptoms in regard to the stress has been emphasized. Although Scandinavian psychiatrists were instrumental in further defining the disorder, an international acceptance has grown, although, in certain cases, culture-specific conditions may limit generalizability.

COMPARATIVE NOSOLOGY Brief psychotic disorder is a new diagnosis in DSM-IV. The diagnosis of brief reactive psychosis was first incorporated into the world psychiatric nomenclature in ICD-8 in 1967 and first appeared in DSM-II in 1968, although neither of those classifications provided distinct diagnostic criteria. In ICD-8 a special class was created, under the title "other psychoses," in which psychotic conditions attributable to a recent life experience were noted. In DSM-II several subtypes were designated: psychotic depressive reaction, reactive excitation, reactive confusion, acute paranoid reaction, and reactive psychosis unspecified. ICD-9 also did not provide criteria.

TABLE 15.1-3
Diagnostic Criteria for Brief Psychotic Disorder

A. Presence of one (or more) of the following symptoms:
   (1) delusions
   (2) hallucinations
   (3) disorganized speech (e.g., frequent derailment or incoherence)
   (4) grossly disorganized or catatonic behavior
   Note: Do not include a symptom if it is a culturally sanctioned response pattern.
B. Duration of an episode of the disturbance is at least one day but less than one month, with eventual full return to premorbid level of functioning.
C. The disturbance is not better accounted for by a mood disorder with psychotic features, schizoaffective disorder, or schizophrenia, and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:
With marked stressor(s) (brief reactive psychosis): if symptoms occur shortly after and apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture
Without marked stressor(s): if psychotic symptoms do *not* occur shortly after, or are not apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture
With postpartum onset: if onset within four weeks postpartum

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It listed brief reactive psychosis as a subtype of other and unspecified reactive psychoses. The disorder was listed in the glossary as a florid psychosis of at least a few hours' duration but not longer than two weeks, having a sudden onset soon after a severe stressor, and involving full recovery to the previous baseline state.

DSM-III described a disorder of sudden onset with a total duration limited to two weeks. It required at least one psychotic symptom, a recognizable precipitating stressor, and a full return to premorbid functioning. DSM-III-R lengthened the duration criterion to include cases lasting up to one month. In addition, the psychotic symptoms needed to occur apparently in response to the stressful life event. That criterion not only emphasized the chronological relationship but also required that a clinical judgment be made about the causal relation. DSM-III-R also adjusted the stressor criteria to allow the precipitant to be a series of events, no one of which was highly stressful but that in aggregate yielded an overwhelming state. DSM-III-R excluded mood disorders, schizotypal personality disorder, and the prodromal symptoms of schizophrenia.

The DSM-III and DSM-III-R diagnostic criteria drew criticism from some investigators, who felt that the concept delineated by Scandinavian psychiatrists had been altered and the criteria made too restrictive. They argued that doing so limited the clinician's ability to study an appropriate cohort of patients. For example, it was unclear what fraction of patients historically met the criteria for emotional turmoil or overwhelming perplexity during the reactive episode. Also, if prodromal symptoms were taken out of the context of schizophrenia, they could be broad and ill-defined, even representing certain elements of personality that made the patient vulnerable to a reactive psychosis. DSM-III-R also contained an apparent contradiction: Schizotypal personality disorder was cited as making patients particularly vulnerable to brief reactive psychosis, yet the diagnostic criteria specifically excluded patients with that personality disorder.

DSM-IV now allows for a broadly defined disorder under the rubric brief psychotic disorder. Cases may be specified to occur in response to marked stressors or not. The exclusion criteria for the prodromal symptoms of schizophrenia and the presence of schizotypal personality disorder have been eliminated. With the duration requirement increased to one month for schizophreniform disorder, those criteria are no longer thought to be necessary to clarify the boundary between the disorders. The criteria for emotional turmoil or overwhelming perplexity and confusion also are no longer required. DSM-IV's criteria allow for increased flexibility of diagnosis and should help reduce the number of cases diagnosed in the residual category of psychotic disorders not otherwise specified. The criteria are also compatible with ICD-10, which uses the general term "acute and transient psychotic disorders," with further subtyping based on the presence of stress, to define reactive psychosis.

EPIDEMIOLOGY Brief psychotic disorder appears to be an uncommon condition. Because of variations in diagnostic criteria and other methodological differences, wide discrepancies exist across studies that have attempted to define the incidence and the prevalence of brief reactive psychosis. It has not been diagnosed often by American psychiatrists, and it was found to be relatively uncommon in DSM field trials. Its onset is most frequently reported in young adults, with the average age at onset being in the late 20s or early 30s, although cases have also been recognized later in life. No reliable data are available on sex, race, or social class associations.

ETIOLOGY Little is known about the etiology of brief psychotic disorder. Historically, the presence of a markedly stressful event was thought to precipitate brief reactive psychosis. Along with posttraumatic stress disorder and adjustment disorders, brief reactive psychosis is one of the few diagnoses in DSM-IV in which a specific causative agent is identified (that is, a psychosocial stressor). However, no well-controlled studies have assessed the causal role of various forms of stress or other factors in causing brief reactive psychosis. Conflict may arise from domestic strife, employment problems, accidents, illness, or the death of a family member. Immigrants may be vulnerable to the condition and may appear in a state of culture shock. The magnitude of a stressor has classically been emphasized, but the cumulative effect of several events may prove to be more important than one event. In addition, the meaning that a specific event has for a person in a given psychosocial setting should be clinically appreciated. Severe intrapsychic conflicts have also been posited as potential triggers for brief psychotic disorder.

Stressors are generally considered to be nonspecific and seem to influence most directly the timing of the onset of the disorder. Many investigators think that preexisting psychopathology helps predispose a patient to its development, and people with paranoid, histrionic, narcissistic, schizotypal, or borderline personality disorders are thought to be particularly vulnerable. Various explanations have been offered, including psychodynamic formulations. For example, some cases of "hysterical psychosis" have been described as an extreme presentation of a hysterical personality disorder in which the ego's ability to function has been overwhelmed by unconscious material that erupts into consciousness. In borderline personality disorder patients, psychotic reactions have been noted at times of threatened abandonment and are seen by some clinicians as an attempt to provide temporary distance in the relationship. Other explanations may involve immature ego development, the use of primitive defenses, and the lack of external supports. A causative role of stress is not assumed, however, in the DSM-IV category of brief psychotic disorder.

A number of family studies have supported a genetic vulnerability to brief reactive psychosis. Although the studies are often limited by methodological flaws, the evidence shows that reactive psychosis tends to run true in families. Although brief psychotic disorder may have a relation to mood disorders, no evidence supports a genetic relation to schizophrenia.

DIAGNOSIS AND CLINICAL FEATURES Patients with brief psychotic disorder have an abrupt onset of impaired reality testing and may present with a variety of associated symptoms, including delusions, hallucinations, bizarre behavior and postures, disorganized speech, and catatonic behavior. Such patients may also appear highly confused and their affect may shift rapidly, although those features are no longer required for diagnostic purposes. In cases of brief reactive psychosis, symptoms can often be understood in the context of the patient's psychosocial surroundings, although the clinician may require some knowledge of different cultures. Culturally sanctioned response patterns are important to recognize and to consider prior to making a diagnosis of brief psychotic disorder. The precipitating event may be a major stress, such as the loss of a loved one or the psychological trauma of combat. Alternatively, a series of life stresses may have the cumulative effect of causing patients to exceed a stress threshold, a point at which they begin to exhibit psychotic symptoms. On cross-sectional viewing, the diagnosis is difficult to differentiate from other types of acute psychosis.

Scandinavian investigators have defined several subtypes of reactions based on the predominant symptoms. The subtypes include acute paranoid reactions, reactive confusions with disturbances in attention and orientation, reactive excitations or manias, and reactive depressive psychosis; the majority of cases in the literature are of the depressive subtype. By definition, the symptoms persist from one day to one month, and the patient usually has a prompt recovery, with a full return to the premorbid level of functioning and personality, which may include a personality type, such as histrionic or borderline, that can predispose to further episodes of brief psychotic disorder.

DIFFERENTIAL DIAGNOSIS Given the often abrupt onset of symptoms, clinicians must consider the possibility of a psychotic disorder due to a general medical condition, a substance-induced psychotic disorder, or delirium. The initial history,

physical examination, and laboratory studies, including a toxicology screen, should help rule out a number of those conditions. When the patient appears confused and unable to sustain attention, the diagnosis of delirium needs to be considered. Further testing with modalities such as CT, magnetic resonance imaging (MRI), or EEG should also be considered.

If the psychiatric disorder persists for more than one month, the diagnosis has to be changed to schizophreniform disorder, schizophrenia, schizoaffective disorder, mood disorder with psychotic features, delusional disorder, or psychotic disorder not otherwise specified. The differential diagnosis between brief psychotic disorder and schizophreniform disorder may be especially difficult to make when the psychotic symptoms have remitted before one month in response to pharmacological treatment. In that case, longitudinal observations to rule out the possibility of a recurrent psychotic disorder should be considered. When symptoms are present for less than one month, the presence of a clear stressor and an abrupt onset suggest brief reactive psychosis (called brief psychotic disorder, with marked stressor, in DSM-IV), but factitious disorder, with predominantly psychological signs and symptoms, may be present (if the symptoms are intentionally produced), and malingering should also be considered. Some personality disorders, such as borderline personality disorders, have transient psychotic symptoms. However, if psychotic symptoms persist for at least one day, an additional diagnosis of brief psychotic disorder may be appropriate. In a few cases a dissociative disorder is a valid diagnosis when the patient is unable to recall personal information as a result of a severe stressor. However, the presence of florid psychotic symptoms makes the diagnosis of dissociative disorder unlikely.

COURSE AND PROGNOSIS By definition, brief psychotic disorder is of short duration (less than one month), and the patient makes a full return to baseline functioning. Follow-up studies have been done mainly in Scandinavia and are limited by methodological flaws, such as retrospective designs. About 50 percent of patients who have received the diagnosis of brief reactive psychosis seem to retain that diagnosis at long-term follow-up. A substantial number of other cases, however, go on to a long-term course and are rediagnosed as schizophrenia or mood disorder. At present, there is no initial way to distinguish brief psychotic disorder from acute-onset schizophrenia or mood disorders with psychotic features. Certain features prognostic of a good outcome have been identified in the literature, although those features have been inconsistent. The good prognostic features include an acute onset of symptoms, good premorbid functioning, the presence of affective symptoms, a short duration of symptoms, and confusion during the episode of psychosis.

A recent study shows a higher mortality risk for patients with brief reactive psychosis than for the population in general. That risk seems to be highest for young patients in the first years after the resolution of the psychotic reaction. Other studies show that some patients experience significant psychosocial disability and suggest the need for continued follow-up after the treatment of the brief psychotic disorder. Few data are available on the recurrence of reactive episodes.

TREATMENT Acute psychotic disorder requires both immediate and long-term treatment. In the short term, patients with the disorder may be a danger to themselves or others, and hospitalization should be considered. Hospitalization facilitates both close observation and a full examination for possible medical conditions. A quiet, well-structured environment with reduced stimulation is usually helpful. At times, behavioral disturbances may necessitate physical or chemical restraints.

No controlled studies are available to guide the clinician in the treatment of the disorder. If medication is necessary, a low dosage of a high-potency antipsychotic, preferably with a prophylactic antiparkinsonism agent, is one option. That regimen reduces the likelihood of acute extrapyramidal side effects, such as akathisia, which has been linked to episodes of agitation and violent behavior. Benzodiazepines are another alternative. They may be used alone or in combination with an antipsychotic. In general, benzodiazepines are safe and may have antipsychotic efficacy in the acute situation. Their use helps minimize patient exposure to antipsychotic medication side effects and may be less likely than the antipsychotics to obscure the clinical situation. However, benzodiazepines can lead to behavioral disinhibition and may create the risk of withdrawal seizures, although the seizures seem to be of greatest concern with prolonged use at high dosages. The role of lithium, antidepressants, and other medications is unclear at this time, although scattered reports favor their use.

Once the acute episode has subsided, the clinician must work with patients to clarify their vulnerability to stress and to enhance their coping mechanisms. The therapist may need to understand a wide array of sociocultural and interpersonal issues, and a tailored treatment plan is needed for each case. Emphasis on problem-solving skills is valuable, and psychotherapy may help strengthen personality weaknesses. Supportive psychotherapy can also help restore the patient's morale and self-esteem. Longer-term therapy is suggested after the acute psychosis has resolved.

In general, maintenance antipsychotic treatment has no role in brief psychotic disorder. If the patient continues to require antipsychotics for many months, an alternative diagnosis should be considered.

A 52-year-old registered nurse was brought to an emergency room by a friend because of visual hallucinations (seeing colors and numbers), referential thinking concerning colors, and persecutory delusions. The patient had been well until one week before, when her family noticed that she started to throw things away, including food, for no apparent reason. One evening she stood in a doorway, staring for several minutes. She had been talking a lot about family problems, including being the sole support for several children, but she was most upset by her brother's recent prison release, fearing that he was going to harm her.

She had no history of drug or alcohol use and no medical problems, and she was using no medications. On two previous occasions she had requested help for anxiety related to different sets of stressors. In each case she remained in treatment for a short period and did not receive medication.

On admission to the hospital, she kept questioning staff member identification cards, and she felt that she was about to be harmed. She displayed a strange gait at times and histrionically demanded to know what the cause was. Her physical examination and laboratory results were unremarkable, as were the findings of brain MRI, EEG, and urine toxicology tests. After receiving lorazepam (Ativan) for several days, her thought disorder improved, and she no longer experienced hallucinations. She was responsive to the ward milieu, benefiting from individual and group therapies. In a family meeting she was able to discuss her concerns and develop effective coping strategies. After her discharge from the hospital, she did well at work and continued in supportive psychotherapy without the need of medication.

SUGGESTED CROSS-REFERENCES

Material relevant to this section is presented in Chapter 14 on schizophrenia and Chapter 16 on mood disorders. Relevant information concerning treatment can be found in Chapter 32 on biological therapies and Chapter 31 on psychotherapies. Psychiatric rehabilitation is discussed in Section 50.4. Psychosocial treatment of schizophrenia is discussed in Section 14.9, and

individual psychotherapy of schizophrenia is discussed in Section 14.10. Psychosocial treatments of mood disorders are discussed in Section 16.8. Psychodynamic concepts relevant to the causes of schizophrenia and mood disorders are found in Section 14.6 and Section 16.5, respectively. Medical illnesses that can lead to mixed states of affective and psychotic symptoms are discussed in Section 26.12 on consultation-liaison psychiatry.

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15.2 DELUSIONAL DISORDER AND SHARED PSYCHOTIC DISORDER

THEO C. MANSCHRECK, M.D.

INTRODUCTION

Delusional disorder is the current classification for a group of disorders of unknown cause, the chief feature of which is the delusion (Table 15.2-1). Although the specific content of the delusion may vary from one case to the next, it is the occurrence of the delusion, its persistence, its impact on behavior, and its prognosis that unify these seemingly different disorders. In considerable agreement with Emil Kraepelin's concept of paranoia, the revised third edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) provided reliable criteria for identifying cases and collecting systematic information about these conditions. That development in classification reestablished the clinical importance of this group of disorders and may have reversed a trend of diagnosing them infrequently. The criteria use the term "delusional" to avoid the ambiguity of the term "paranoid" used earlier in the third edition of DSM (DSM-III) classification, "paranoid disorders," and to emphasize that the category includes disorders in which delusions other than those of the persecutory or jealous type are present. The fourth edition of DSM (DSM-IV) attempts to refine the definitions and the boundaries with other disorders, including substance-induced disorders, mental disorders due to general medical conditions, mood disorders, and schizophrenia. The DSM-IV definition, like its predecessors, hinges on the presence of a nonbizarre delusion. DSM-IV acknowledges the difficulty of judging whether a delusion is bizarre, meaning clearly

TABLE 15.2-1
DSM-IV Definition of Delusion and Certain Common Types Associated with Delusional Disorders

delusion A false belief based on incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of the person's culture or subculture (e.g., it is not an article of religious faith). When a false belief involves a value judgment, it is regarded as a delusion only when the judgment is so extreme as to defy credibility. Delusional conviction occurs on a continuum and can sometimes be inferred from an individual's behavior. It is often difficult to distinguish between a delusion and an overvalued idea (in which case the individual has an unreasonable belief or idea but does not hold it as firmly as is the case with a delusion).

Delusions are subdivided according to their content. Some of the more common types are listed below:

bizarre—A delusion that involves a phenomenon that the person's culture would regard as totally implausible.
delusional jealousy—The delusion that one's sexual partner is unfaithful.
erotomanic—A delusion that another person, usually of higher status, is in love with the individual.
grandiose—A delusion of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person.
mood-congruent *See* mood-congruent psychotic features.
mood-incongruent *See* mood-incongruent psychotic features.
of being controlled—A delusion in which feelings, impulses, thoughts, or actions are experienced as being under the control of some external force rather than being under one's own control.
of reference—A delusion whose theme is that events, objects, or other persons in one's immediate environment have a particular and unusual significance. These delusions are usually of a negative or pejorative nature, but also may be grandiose in content. This differs from an *idea of reference*, in which the false belief is not as firmly held nor as fully organized into a true belief.
persecutory—A delusion in which the central theme is that one (or someone to whom one is close) is being attacked, harassed, cheated, persecuted, or conspired against.
somatic—A delusion whose main content pertains to the appearance or functioning of one's body.
thought broadcasting—The delusion that one's thoughts are being broadcast out loud so that they can be perceived by others.
thought insertion—The delusion that certain of one's thoughts are not one's own, but rather are inserted into one's mind.
mood-congruent psychotic features—Delusions or hallucinations whose content is entirely consistent with the typical themes of a depressed or manic mood. If the mood is depressed, the content of the delusions or hallucinations would involve themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. The content of the delusion may include themes of persecution if these are based on self-derogatory concepts such as deserved punishment. If the mood is manic, the content of the delusions or hallucinations would involve themes of inflated worth, power, knowledge, or identity, or a special relationship to a deity or a famous person. The content of the delusion may include themes of persecution if these are based on concepts such as inflated worth or deserved punishment.
mood-incongruent psychotic features—Delusions or hallucinations whose content is not consistent with the typical themes of a depressed or manic mood. In the case of depression, the delusions or hallucinations would not involve themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. In the case of mania, the delusions or hallucinations would not involve themes of inflated worth, power, knowledge, or identity, or a special relationship to a deity or a famous person. Examples of mood-incongruent psychotic features include persecutory delusions (without self-derogatory or grandiose content), thought insertion, thought broadcasting, and delusions of being controlled whose content has no apparent relationship to any of the themes listed above.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

implausible, not understandable, and not derived from ordinary life experiences. In contrast, the nonbizarre delusion involves situations or circumstances that can occur in real life (for example, being followed, infected, or deceived by a lover). DSM-IV also emphasizes the differential diagnosis of schizophrenia, mood disorders, substance-induced disorders, and mental disorders due to a general medical condition before the diagnosis of delusional disorders can be made. Those conceptual refinements and demarcations from other conditions have increased the usefulness of the delusional disorder criteria.

Despite those advances, clinicians are relatively unaware of delusional disorders. There are several possible reasons. Persons with the conditions do not regard themselves as mentally ill and actively oppose psychiatric referral. Because they may experience little impairment, they generally remain outside hospital settings, appearing reclusive, eccentric, or odd, rather than ill. If they do have contact with professionals, it is more likely to be with lawyers regarding litigious concerns; with medical specialists regarding health concerns; or with the police regarding complaints of trespass, persecution, or threat, rather than psychiatric clinicians regarding complaints of emotional disorder. It is a hallmark of those disorders that the patient does not believe that he or she is deluded or in need of psychiatric assistance. In the infrequent psychiatric encounter the tendency among clinicians is to diagnose them as other conditions, often schizophrenia or mood disorders.

Delusional disorders are uncommon, but probably not as rare as previously thought. While many individuals with such disorders seek assistance from medical specialists, judges, or the police, they are increasingly being recognized as psychiatrically ill. The relationship of these disorders to other psychoses remains unclear, and much about them is a puzzle. The DSM-IV requirement of excluding other conditions is prudent given the special importance of differential diagnosis. Though the DSM-IV criteria are not definitive, they have provided a sound basis for clinical and research investigation. Systematic studies based on larger samples of these disorders are needed to anchor classification with sound information, although such studies may be difficult to achieve. A biological basis for these disorders is proposed on many grounds, but its definition has been elusive and remains distant.

DEFINITION

DELUSIONAL DISORDER According to DSM-IV, the diagnosis of delusional disorder can be made when a person exhibits nonbizarre delusions of at least one month's duration that cannot be attributed to other psychiatric disorders. Definitions of the term "delusion" and types relevant to delusional disorders are presented in Table 15.2-1. Diagnostic criteria for delusional disorder are presented in Table 15.2-2. Nonbizarre means that the delusions must be about situations that can occur in real life, such as being followed, infected, loved at a distance, and so on. There are several types of delusions, and the predominant type is specified when making the diagnosis.

In general, the patient's delusions are well systematized and have been logically developed. The person may experience auditory or visual hallucinations, but those are not prominent features. Tactile or olfactory hallucinations may be both present and prominent if they are related to the delusional content or theme. The sensation of being infested by bugs, associated with delusions of infestation, and the belief that one's body odor is foul, associated with somatic delusions, are examples. The per-

TABLE 15.2-2
Diagnostic Criteria for Delusional Disorder

A. Nonbizarre delusions (i.e., involving situations that occur in real life, such as being followed, poisoned, infected, loved at a distance, or deceived by spouse or lover, or having a disease) of at least 1 month's duration.
B. Criterion A for schizophrenia has never been met. Note: Tactile and olfactory hallucinations may be present in delusional disorder if they are related to the delusional theme.
C. Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired and behavior is not obviously odd or bizarre.
D. If mood episodes have occurred concurrently with delusions, their total duration has been brief relative to the duration of the delusional periods.
E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify type (the following types are assigned based on the predominant delusional theme):
Erotomanic type: delusions that another person, usually of higher status, is in love with the individual
Grandiose type: delusions of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person
Jealous type: delusions that the individual's sexual partner is unfaithful
Persecutory type: delusions that the person (or someone to whom the person is close) is being malevolently treated in some way
Somatic type: delusions that the person has some physical defect or general medical condition
Mixed type: delusions characteristic of more than one of the above types but no one theme predominates
Unspecified type

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TABLE 15.2-3
Diagnostic Criteria for Shared Psychotic Disorder

A. A delusion develops in an individual in the context of a close relationship with another person(s), who has an already-established delusion.
B. The delusion is similar in content to that of the person who already has the established delusion.
C. The disturbance is not better accounted for by another psychotic disorder (e.g., schizophrenia) or a mood disorder with psychotic features and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

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son's behavioral and emotional responses to the delusion appear to be appropriate. Impairment of functioning or personality deterioration is minimal, if it occurs at all. General behavior is neither obviously odd nor bizarre.

SHARED PSYCHOTIC DISORDER Shared psychotic disorder is defined in Table 15.2-3. This unusual condition has also been called *folie à deux* and induced psychotic disorder. It develops in an individual in the context of a close relationship with another person who has an established delusion, and requires an absence of psychotic disorder prior to the onset of the induced delusion. It has usually been classified with paranoid disorders.

HISTORY OF THE PARANOID CONCEPT

Nineteenth century psychiatry devoted much attention to the description of paranoid disorders, in which delusions are a cardinal feature. Karl Ludwig Kahlbaum's description of paranoia in 1863 was the first in a series of contributions that culminated in the classification of paraphrenia, *folie à deux*, morbid jealousy, the better known schizophrenias, and mania. His work also led to a recognition that paranoid features are nonspecific characteristics of many diseases. Subsequent work has led to refined criteria for paranoid and related disorders and has reestablished awareness of less common paranoid presentations such as delusional disorder.

Many clinicians remember being taught that paranoia is so rare that most would not examine a single patient during an entire career. That widespread belief has compromised interest in paranoid disorders. The fact that most persons with delusional disorder live in the community and do not generally seek psychiatric care have made it difficult to carry out systematic case studies. Indeed, knowledge of these conditions has been scanty and frequently anecdotal. However, case series such as those of Alistair Munro (for delusional disorder, somatic type, or for hypochondriacal delusional disorder) or those of Nils Retterstol have been influential in shaping understanding and awareness. What they tell us is that there are persons with these disorders, that the disorders are complex forms of psychiatric illness, and that much remains to be learned.

A major change in the classification of delusional disorders in DSM-III-R and DSM-IV has been to emphasize the central role of delusions in those disorders and to steer away from the vague label of paranoid, which has become synonymous with suspicious. Indeed, suspiciousness may be less common than expected in those disorders. The history of the concept of paranoia indicates that lack of clarity in its use is not new. The word "paranoia" was coined by the ancient Greeks from roots meaning beside and self. Hippocrates applied this term to delirium associated with high fever, but other writers used it to describe demented conditions and madness. It sometimes meant thinking amiss, folly, and the like. Hence, its meaning was unclear. For centuries the term fell into disuse until a revival of interest in the 19th century.

Kahlbaum in 1863 classified paranoia as a separate mental illness: "a form of partial insanity, which, throughout the course of the disease, principally affected the sphere of the intellect." Influenced by the new scientific methods of empirical medicine, Kahlbaum emphasized the importance of natural history in mental illness and restricted the term paranoia to a persistent delusional illness that remained largely unchanged throughout its course. Delusions, he noted, could occur in other medical and psychiatric conditions.

Kraepelin found the paranoid concept troublesome and altered his thinking on it with each edition of his textbook. His final view advocated three types of paranoid disorder. Like Kahlbaum, Kraepelin based his conclusions on analysis of the natural history of mental disorders, particularly on outcome. He restricted the definition of paranoia to an uncommon, insidious, chronic illness (he saw 19 cases during his career) characterized by a fixed delusional system, an absence of hallucinations, and a lack of deterioration of the personality. The types of delusions noted included persecutory, grandiose, somatic, jealous, and possibly hypochondriacal. He considered this illness to derive from defects in the capacity of judgment, a disorder of personality caused by constitutional factors and environmental stress. Paraphrenia was a second paranoid disorder that developed later than dementia precox and was milder. There were hallucinations (auditory in particular) but no mental deterioration (dementia). Finally, there was dementia paranoides, an illness

that initially resembled paranoia but had an earlier onset and showed a deteriorating course. Because of this latter feature Kraepelin considered dementia paranoides a form of dementia precox that arose from disorders of thought, cognition, and emotion. Kurt Mayer's follow-up of Kraepelin's 78 paraphrenia cases challenged the validity of this category because the vast majority in fact showed an outcome indistinguishable from that of dementia precox, casting doubt on the separability of this group. Karl Kolle's follow-up of Kraepelin's paranoia cases indicated some overlap with dementia precox. Kraepelin also emphasized that isolated paranoid symptoms occurred in a variety of psychiatric and medical illnesses.

Eugen Bleuler also recognized paranoia (though he broadened its definition to include cases with hallucinations); a paranoid form of dementia precox, which he called schizophrenia; and an intermediate group, but thought that the paranoia described by Kraepelin was so rare that it did not warrant a separate classification. Further, he argued that schizophrenic symptoms must be suspected and carefully sought after even in those cases. Paraphrenia and intermediate conditions, he held, were forms of schizophrenia linked by "much that was identical," and in particular a common disturbance in associative processes. He also emphasized that paranoid symptoms occurred in other conditions and that to label them schizophrenic required at least one of the fundamental symptoms: loosened associations, ambivalence, inappropriate affect, and autism.

Sigmund Freud used the autobiographical writings of Judge Daniel Schreber to illustrate the role of psychological defense mechanisms in the development of paranoid symptoms. He proposed that Schreber's illness involved a process of denial or contradiction of repressed homosexual impulses toward his father. Persecutory and other delusions result from projecting these denied yearnings into the environment. He did not differentiate subtypes of paranoid disorder, and he added to the confusion by proposing that the term "paraphrenia" be substituted for dementia precox or schizophrenia. The major impact of Freud's work was to suggest hypotheses that indicated the relationship between certain delusions and personality.

Ernst Kretschmer's work on the theory of paranoia emphasized that certain sensitive personalities, characterized by depressive, pessimistic, and narcissistic traits, developed paranoid features acutely when key or precipitating experiences occurred at critical moments in their lives. He observed that those individuals did not develop schizophrenia and had a favorable prognosis. A number of other observers, predominantly but not exclusively European (for example, the American concept of hysterical psychosis) proposed connections between personality and delusion development. Those efforts, based on various theories of course of paranoid disturbance, have persisted despite modest empirical support. Out of such work have come terms, such as reactive and psychogenic psychosis, which have figured in various classification schemes, adding further confusion to the effort to bring about international consistency in definition.

Current views are based on those historical antecedents. DSM-III introduced greater rigor in the assessment by requiring clearer criteria boundaries among the varied disorders with delusions. And the awareness that delusions result from numerous conditions has had a positive influence on the diagnostic process. Yet much of current clinical and research writing on paranoid conditions has characteristically avoided defining the term "paranoid," apparently because it has assumed that everyone knows what paranoid means. In popular and literary usage the term "paranoid" has come to mean insane, angrily suspicious, distrustful, or irrationally irritable. The paranoid concept, however clumsy it may be, continues to be used in clinical work. Because it is necessary to differentiate conditions with paranoid features, a useful concept of the term is fundamental.

SHARED PSYCHOTIC DISORDER Jules Baillarger first described the syndrome, calling it *folie à communiquée*, in 1860, although the first description is commonly attributed to Ernest Charles Lasègue and Jules Falret, who described the condition in 1877 and gave it the name of *folie à deux*. The syndrome has also been called communicated insanity, contagious insanity, infectious insanity, psychosis of association, and double insanity. Marandon de Montyel divided *folie à deux* into three groups (*folie imposée, folie simultanée,* and *folie communiquée*), and Heinz Lehmann added a fourth group, *folie induite.*

CLARIFICATION OF THE PARANOID CONCEPT

Paranoid features (signs and symptoms) are among the most dramatic and serious disturbances in psychiatry and medicine. Nevertheless, the term "paranoid" refers to a variety of behaviors that are often not psychopathological and are not necessarily related to schizophrenia. Hence, the meaning of the term "paranoid" has become obscure. Some clinicians label ordinary suspiciousness paranoid. Others restrict use of the term to persecutory delusions. Still others apply the term only to grandiose, litigious, hostile, and jealous behavior, despite the fact that those behaviors may be within the normal behavioral spectrum. To make the paranoid concept useful and less vague requires the consideration of several points.

1. The term "paranoid" is a clinical construct used to interpret observations, and in order to apply this construct effectively, the clinician must know its meaning and be able to make accurate observations of potentially paranoid behavior.
2. Use of the term "paranoid" means the clinician has judged that the person's behavior is psychopathological. This judgment is usually based on the discovery that the person who displays such features is either disturbed or disturbing to others.
3. Although many contributions to understanding paranoid phenomena have focused on conditions in which paranoid features are central (for example, schizophrenia for Bleuler, paranoia for Kraepelin, and dementia paranoides), those features are not necessarily associated with schizophrenia and can appear in other psychiatric and medical disorders. Hence, paranoid features indicate psychopathology, but no specific cause (Table 15.2-4), chronicity, or curability.
4. The observations that form the basis for judging behavior to be paranoid are of two kinds: subjective (part of the private mental experience of the patient, for example, a delusion) and objective (observable as a manifest form of behavior, such as litigiousness, guardedness, grandiosity). Table 15.2-5 is a list of the subjective and objective features that have traditionally been labeled paranoid and that are frequently found in association. Some can be manifestations of normal behavior. The judgment that such features are paranoid may rest on their extremeness or inappropriateness, their presence in combination or association with other behaviors on the list, and the presence of delusions.
5. The term paranoid delusions has traditionally referred to a wide variety of delusions, not simply those of grandeur, persecution, or jealousy. Because of recent confusion that term probably should not be used. The term "paranoid" and associated terms are defined in Table 15.2-6.

TABLE 15.2-4
Conditions and Agents Associated with Delusions and Other Paranoid Features

Neurological disorders
- Arteriosclerotic psychoses
- Blunt head trauma
- Brain tumors
- Cerebrovascular disease
- Delirium
- Dementia
- Fat embolism
- Hearing loss
- Huntington's chorea
- Hydrocephalus
- Hypertensive encephalopathy
- Idiopathic basal ganglia calcification
- Idiopathic Parkinson's disease
- Intracranial hemorrhage
- Marchiafava-Bignami disease
- Menzel-type ataxia
- Metachromatic leukodystrophy
- Migraine
- Motor-neuron disease
- Multiple sclerosis
- Muscular dystrophy
- Narcolepsy
- Postencephalitic parkinsonism
- Presenile psychoses (Alzheimer's and Pick's diseases)
- Roussy-Levy syndrome
- Senile psychoses
- Spinocerebellar degeneration
- Subarachnoid hemorrhage
- Subdural hematoma
- Temporal lobe epilepsy

Metabolic and endocrine disorders
- Acute intermittent porphyria
- Addison's disease
- Complication of surgical portacaval anastomosis for cirrhosis
- Cushing's syndrome
- Folate deficiency
- Hemodialysis
- Hypercalcemia
- Hypoglycemia
- Hyponatremia
- Hypopituitarism
- Liver failure
- Malnutrition
- Niacin deficiency
- Pancreatic encephalopathy
- Parathyroid disorders
- Pellagra
- Pernicious anemia
- Phenylketonuria
- Systemic lupus erythematosus
- Thiamine deficiency
- Thyroid disorders
- Uremia
- Vitamin B_{12} deficiency
- Wilson's disease

Sex chromosome disorders
- 47 XXY
- Klinefelter's syndrome
- Turner's syndrome

Infections
- Acquired immune deficiency syndrome
- Encephalitis lethargica
- Creutzfeldt-Jakob disease
- Malaria
- Syphilis
- Toxic shock syndrome
- Trypanosomiasis
- Typhus
- Viral encephalitides

Psychiatric disorders
- Brief psychotic disorder
- Delusional disorder (including classic paranoia)
- Shared psychotic disorder
- Mood disorders
- Schizoaffective disorder
- Schizophrenia (all subtypes)
- Schizophreniform disorder

Alcohol and drugs
- Alcohol withdrawal
- Amphetamine
- Anesthetic nitrous oxide
- Atropine toxicity
- Barbiturate
- Chronic alcohol hallucinosis
- Chronic bromide intoxication
- Cocaine
- Ephedrine
- Marijuana
- Mescaline and other hallucinogens
- Perbitine
- Withdrawal from minor tranquilizers and hypnotic medications

Toxic agents
- Arsenic
- Carbon monoxide
- Manganese
- Mercury
- Thallium

Pharmacological agents
- Adrenocorticotropic hormone
- Amphetamine and related compounds
- Anticholinergic drugs
- Antimalarials
- Antitubercular drugs
- Bromocriptine
- Bupropion
- Cimetidine
- Cortisone
- Diphenylhydantoin
- Disulfiram
- L-Dopa
- Imipramine and other tricyclic antidepressants
- Mephentermine
- Methyldopa and imipramine (combination)
- Methyltestosterone
- Pentazocine
- Phenylpropanolamine
- Propylhexedrine

COMPARATIVE NOSOLOGY

Certain advances have been made in the nosology of delusional disorders, but the variety of current definitions illustrates that consensus has not yet been achieved. The reasons for such differences are multiple. The principal reason is simply a lack of relevant data; delusional disorders occur infrequently or are easily misdiagnosed and have minimal overt identifying characteristics. Because only limited knowledge, largely from case reports, has accumulated; systematic, larger scale studies are uncommon. Those studies that exist have generally been European and have employed varied classifications. Also, the fundamental concept that the disorders are distinct from schizophrenia and mood disorders has until recently been unacceptable to many psychiatrists.

Kahlbaum was the first to use the term paranoia to designate a diagnostically separate group of disorders. Kraepelin developed this diagnostic concept further by emphasizing the chronic and unremitting nature of paranoia and the lack of other features such as hallucinations that distinguished it from schizophrenia. The first diagnostic manual of the American Psychiatric Association (DSM-I) incorporated those ideas in 1952 and defined paranoid reactions as conditions in which there are persecutory or grandiose delusions, with emotional responses and behavior consistent with the delusions, but generally lacking hallucinations. The subtypes were paranoia (a chronic disorder with sys-

TABLE 15.2-5
Paranoid Features

Objective features
Anger
Critical, accusatory behavior
Defensiveness
Grandiosity or excessive self-importance
Guardedness, evasiveness
Hate
Hostility
Humorlessness
Hypersensitivity
Inordinate attention to small details
Irritability, quick annoyance
Litigiousness (letter writing, complaints, legal action)
Obstinacy
Resentment
Seclusiveness
Self-righteousness
Sullenness
Suspiciousness
Violence, aggressiveness
Subjective features*
Delusions of self-reference, persecution, grandeur, infidelity, love, jealousy, imposture, infestation, disfigurement
Overvalued ideas

*Part of private mental experience. The patient often discloses those features during the clinical interview, but may not do so, even with specific questioning.

tematized delusions) and paranoid state (a more acute, less persistent condition with less systematized delusions). The second edition of DSM (DSM-II) in 1968 largely preserved these concepts.

DSM-III Although new definitions were established in DSM-III in 1980, earlier concepts are still evident. The essential features of paranoid disorders in DSM-III are persistent persecutory delusions or delusional jealousy not due to any other mental disorder. Included in the group of paranoid disorders were paranoia; shared paranoid disorder; acute paranoid disorder; and a residual category, atypical paranoid disorder. The boundaries between these conditions and other disorders, such as paranoid personality disorder or paranoid schizophrenia, were noted to be vague. Different types of paranoid disorders were classified on the basis of chronicity. The criteria narrowed the bounds of previous classifications by not including cases with marked hallucinations or certain delusions (for example, hypochondriacal, erotomania, and others).

DSM III-R In 1987, DSM-III-R simplified the DSM-III definition, attempted to minimize the confusion associated with the term paranoid, and highlighted the view that the formation of delusions in the absence of schizophrenia, mood disorder, or organic disorder is the essential feature of these conditions. In contrast to DSM-III, diagnosis in DSM-III-R and DSM-IV requires a one-month's duration of symptoms. Subtyping is based on the predominant type of delusion, which is specified (such as jealous, erotomanic, somatic). This latter feature broadens the category to include a variety of unusual delusions as well as the more common persecutory type. In many respects these criteria are virtually identical to Kraepelin's formulation of paranoia. The two exceptions were Kraepelin's reluctance to endorse a subtype of somatic or hypochondriacal paranoia or to permit cases with hallucinations to be given this diagnosis. He believed cases with hypochondriacal delusions rarely occurred alone.

Shared paranoid disorder was renamed induced psychotic disorder in DSM-III-R and was placed in the category psychotic disorders not elsewhere classified, along with schizophreniform and schizoaffective disorders and brief reactive psychosis. This represents a fundamental departure from DSM-III, which placed this disorder in the paranoid disorders. In patients with this disorder, the delusional content may concern not only persecution or jealousy but virtually any form of delusion, hence, the change in terminology. The term "induced" may more accurately describe the nature of the condition, but hardly resolves the puzzle of causation.

DSM-IV

DELUSIONAL DISORDER DSM-IV makes modest changes in the DSM-III-R criteria in attempting to refine the definition

TABLE 15.2-6
Terminology Connected with Paranoia

Term	Description
Delusional disorders	DSM-III-R category emphasized that the cardinal feature of these conditions is delusions; DSM-IV criteria is one or more nonbizarre delusion lasting for more than one month
Paranoia	Old term for an insidiously developed disorder in which persons suffer from an unshakable delusional system but have no disturbance in the clarity or form of their thinking; also known as paranoia vera, simple delusional disorder, delusional monomania
Paranoic or paranoiac	Old adjectives used to describe persons with paranoia
Paranoid	Broad term meaning suspicious to most people. In psychiatry it is a clinical construct used to describe various objective and subjective features of behavior deemed to be psychopathological (Table 15.2-5); refers to no specific condition (e.g., to be paranoid does not mean that schizophrenia is present)
Paranoid delusion	Older term used to refer to persecutory and grandiose delusions because of their occurrence in the paranoid subtype of schizophrenia; this term has suffered from the confusion associated with the paranoid concept; DSM-III-R recommended that it no longer be used
Paranoid disorders	DSM-III term for an idiopathic group of conditions including paranoia, acute paranoid disorder, shared paranoid disorder, and atypical paranoid disorder; no longer used
Paranoid personality	Enduring traits of paranoid behavior not due to schizophrenia or other mental disorder; generally, there is no evidence of delusions or other features of psychosis
Paranoid syndrome	Term applied to constellations of paranoid features that occur together and can arise from multiple sources, including depression, general medical condition, substance-induced disorders, and schizophrenia
Paraphrenia	Old term for conditions lying theoretically between schizophrenia and paranoia and sharing features of both (hallucinations but no deterioration). It, too, remains controversial and probably should not be used until research validates its meaning

of delusional disorders. In DSM-III-R, the distinction between schizophrenia and delusional disorders had been unclear and controversial. In DSM-III-R, this boundary was defined by the nonbizarre qualities of delusions in delusional disorder and the absence of other active phase symptoms of schizophrenia. Also important was the required absence of other odd or bizarre behavior apart from the delusion. Because the distinction between bizarre and nonbizarre is difficult to define and therefore to apply reliably, other terms such as systematized and prominent were suggested. In practice, however, those terms also have limitations. The quandary has helped promote the case for modifying the criteria in another way: specifically, to use the level of impaired functioning as a means of characterizing the distinction between schizophrenia and delusional disorders. However, given the variability of outcomes in both disorders, this strategy also has limitations. In DSM-IV the suggestion is made that when poor functioning occurs in delusion disorder, it is the result of the delusional beliefs themselves. For example, a person quits a job because he or she believes that the fumes in the workplace are causing a cancerous growth. That person's financial situation worsens with repeated medical consultations. In contrast, poor functioning in schizophrenia is the result of positive and negative symptoms, especially avolition. The resolution of how to make modifications, however, must rest on the effectiveness of the criteria in defining homogeneous and valid subsets of psychotic disordered patients. For this purpose field trials and data analyses have been used to inform the decision scientifically. While the DSM-IV criteria reflect some progress, their validity remains only partly established.

SHARED PSYCHOTIC DISORDER DSM-IV renamed the DSM-III-R category induced psychotic disorder (shared paranoid disorder), calling it shared psychotic disorder. That change reflects the attempt to avoid the term "paranoid" and to identify the condition without reference to any presumed cause or mechanism. The criteria incorporate efforts to define the boundaries between this condition and more common ones, such as other psychotic disorders, mood disorders with psychotic features, substance-induced psychotic disorder, and psychotic disorder due to a general medical condition.

ICD The ninth revision of *International Classification of Diseases and Related Health Problems* contained a larger number of categories for paranoid disorder than the American schemes. Most paranoid disorders fall under the rubric paranoid state, including simple paranoid state, paranoia, paraphrenia, and induced psychosis. Additional subcategories include other and unspecified paranoid states. Acute paranoid reactions and psychogenic paranoid psychosis are classified separately. DSM-III, DSM-III-R, and DSM-IV generally reflect an atheoretical position with respect to the causes of these disorders, whereas ICD-9 was less neutral. For example, psychogenic paranoid psychosis implies a kind of causal mechanism. The categories of paranoid disorder according to these classifications are summarized in Table 15.2-7.

In the tenth revision of ICD (ICD-10), more attention has been paid to creating classifications similar to DSM-III-R and DSM-IV (Table 15.2-8). Paraphrenia, for example, is subsumed under delusional disorder. On the other hand, delusions must be present for about three months to diagnose delusional disorder. For those conditions of less duration, acute and transient psychotic disorder is diagnosed.

EPIDEMIOLOGY

Delusional disorder has been considered an uncommon, if not rare, condition from its earliest descriptions. Epidemiological information is meager. Recent demographic evidence covering a period from 1912 to the 1970s provides an estimate of incidence, prevalence, and related statistics (Table 15.2-9). However, this evidence was assembled using definitions that are not the same as those of DSM-III, DSM-III-R, or DSM-IV. Subsequent data will in all likelihood be somewhat different using the newer criteria. Clearly, the estimates are merely indications, but can be useful guidelines to future appraisals.

Certain features of the data are, nevertheless, remarkable. For example, the stability of estimated incidence has been striking over extended periods of time in this century. The prevalence of these disorders substantiates the widely held clinical impression that they are uncommon conditions (compared with mood disorders and schizophrenia) but are not rare. Most studies indicate that the disorder accounts for 1 to 2 percent of inpatient psychiatric admission. Patients with delusional disorders are somewhat more likely to be women, (but this is an inconsistent feature) and to be relatively more disadvantaged socially and educationally compared to patients with mood disorders. There

TABLE 15.2-7
Comparative Nosology of Delusional Disorder

ICD-9 (1979)	DSM-III (1980)	DSM-III-R (1987)	ICD-10 (1992)	DSM-IV (1994)
Paranoid state, simple	—	—	Delusional disorder	—
Paranoia	Paranoia	Delusional (paranoid) disorder	Delusional disorder	Delusional disorder
Paraphrenia (involuntional paranoid state; late paraphrenia)	—	—	Delusional disorder	—
Induced psychosis (folie à deux, induced paranoid disorder)	Shared paranoid disorder	Induced psychotic disorder	Induced delusional disorder	Shared psychotic disorder
Other specified states (paranoia querulans, Sensitiver Beziehungswahn)	—	—	Delusional disorder	—
Unspecified paranoid states	Atypical paranoid disorder	—	Persistent delusional disorder, unspecified	—
Acute paranoid reaction (bouffée délirante)	Acute paranoid disorder	—	Paranoid reaction	—
Psychogenic paranoid psychosis (protracted reactive paranoid psychosis)	—	—	—	—

is suggestive evidence that immigrant status is associated with delusional disorder. Yet all such observations remain subject to the need for unambiguous replication.

ETIOLOGY

The cause of delusional disorders is unknown. Paranoid features, including the types of delusions encountered in these disorders, occur in a large (and growing) number of conditions (Table 15.2-4). Differences in approach to classifying idiopathic delusional disorder add to the problems of understanding causation. Theories and explanations of delusions abound in the literature; empirical evidence to support those theories is limited. With so many uncertainties, conclusions concerning the cause of delusional disorder must be modest.

The problem can be stated in this fashion. We are dealing with an uncommon, probably heterogeneous, group of illnesses, the validity of which has been questioned since Kahlbaum published his views. The major phenomenologic feature of these conditions is the formation and persistence of delusions. It is well known that delusions occur in a variety of psychiatric and medical conditions, the pathogenesis of which is not fully understood. Hence, discussion of etiology in the delusional disorders can proceed on two lines: (1) the distinctiveness of the category itself, and (2) the theories proposed to account for delusion formation per se.

DISTINCTIVENESS OF DELUSIONAL DISORDER An issue that is central to attributing causation is whether delusional disorder represents a separate group of conditions or, instead, atypical forms of schizophrenic and mood disorders. The relevant data come from a limited number of studies. Despite this, certain consistencies are apparent. Epidemiological data suggest that delusional disorder is a separate condition: delusional disorder is far less prevalent than schizophrenic or mood disorders; age of onset is later than in schizophrenia; and the sex ratio is different from that of mood disorder, which occurs primarily in women. Findings from family or genetic studies also support the concept of separateness. If delusional disorder is simply an unusual form of schizophrenic or mood disorder, the incidence of these latter conditions in family studies of delusional disorder patients should be higher than that of the general population. However, this has not been a consistent finding. Moreover, a recent study concluded that patients with delusional disorder are more likely to have family members who show suspiciousness, jealousy, secretiveness, even paranoid illness, than families of controls. Other investigative efforts have found paranoid personality disorder and avoidant personality disorder to be more common in relatives of delusional disorder patients than in relatives of controls or of schizophrenic patients.

Natural history investigations also lend support to the separateness of the delusional disorder category. Though fraught with methodological shortcomings, premorbid personality data indicate that schizophrenic patients and patients with delusional disorder differ early in life. The former are more likely to be introverted, schizoid, and submissive; the latter, more extroverted, dominant, and hypersensitive. Delusional disorder patients may have below average intelligence. Precipitating factors, especially related to social insolation, conflicts of conscience, and immigration, are more closely associated to delusional disorder than schizophrenia. These characteristics support Kraepelin's view that environmental factors may have an important etiological role. Recent observations of successful treatment with pimozide (Orap) in several subtypes of delusional disorders suggest the possibility of a common pathogenetic mechanism in these disorders. Follow-up studies indicate that the diagnosis of delusional disorder remains stable: only a small proportion of cases (3 to 22 percent) are diagnosed later as schizophrenia, and even fewer (6 percent) are diagnosed later as a mood disorder. Outcome in terms of hospitalization and occupational adjustment are markedly more favorable for delu-

TABLE 15.2-8
ICD-10 Diagnostic Criteria for Persistent Delusional Disorders

Persistent Delusional Disorders
This group includes a variety of disorders in which long-standing delusions constitute the only, or the most conspicuous, clinical characteristic and which cannot be classified as organic, schizophrenic, or affective. They are probably heterogeneous, and have uncertain relationships to schizophrenia. The relative importance of genetic factors, personality characteristics, and life circumstances in their genesis is uncertain and probably variable.

Delusional Disorder
This group of disorders is characterized by the development either of a single delusion or of a set of related delusions which are usually persistent and sometimes lifelong. The delusions are highly variable in content. Often they are persecutory, hypochondriacal, or grandiose, but they may be concerned with litigation or jealousy, or express a conviction that the individual's body is misshapen, or that others think that he or she smells or is homosexual. Other psychopathology is characteristically absent, but depressive symptoms may be present intermittently, and olfactory and tactile hallucinations may develop in some cases. Clear and persistent auditory hallucinations (voices), schizophrenic symptoms such as delusions of control and marked blunting of affect, and definite evidence of brain disease are all incompatible with this diagnosis. However, occasional or transitory auditory hallucinations, particularly in elderly patients, do not rule out this diagnosis, provided that they are not typically schizophrenic and form only a small part of the overall clinical picture. Onset is commonly in middle age but sometimes, particularly in the case of beliefs about having a misshapen body, in early adult life. The content of the delusion, and the timing of its emergence, can often be related to the individual's life situation, e.g. persecutory delusions in members of minorities. Apart from actions and attitudes directly related to the delusion or delusional system, affect, speech, and behavior are normal.

Diagnostic Guidelines
Delusions constitute the most conspicuous or the only clinical characteristic. They must be present for at least three months and be clearly personal rather than subcultural. Depressive symptoms or even a full-blown depressive episode may be present intermittently, provided that the delusion persists at times when there is no disturbance of mood. There must be no evidence of brain disease, no or only occasional auditory hallucinations, and no history of schizophrenic symptoms (delusions of control, thought broadcasting, etc.).

Includes: paranoia
paranoid psychosis
paranoid state
paraphrenia (late)
sensitiver Beziehungswahn

Excludes: paranoid personality disorder
psychogenic paranoid psychosis
paranoid reaction
paranoid schizophrenia

Other Persistent Delusional Disorders
This is a residual category for persistent delusional disorders that do not meet the criteria for delusional disorder. Disorders in which delusions are accompanied by persistent hallucinatory voices or by schizophrenic symptoms that are insufficient to meet criteria for schizophrenia should be coded here. Delusional disorders that have lasted for less than three months should, however, be coded, at least temporarily, under acute and transient psychotic disorders.

Includes: delusional dysmorphophobia
involutional paranoid state
paranoia querulans

Persistent Delusional Disorder, Unspecified

Table from World Health Organization: *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.* World Health Organization, Geneva, 1992. Used with permission.

TABLE 15.2-9
Epidemiological Features of Delusional Disorder

Incidence*	0.7–3.0
Prevalence*	24–30
Age at onset (range)	35–45 (18–80)
Sex ratio M:F	0.85

Table adapted from K S Kendler: Demography of paranoid psychosis (delusional disorder). Arch Gen Psychiatry *39:* 890, 1982.
*Incidence and prevalence figures represent cases per 100,000 population.

sional disorder than for schizophrenic disorder. As previously noted, when social or occupational functioning is poor in delusional disorder, it occurs as the result of the delusional beliefs themselves, not because of negative symptoms.

The evidence argues for distinctiveness of delusional disorder, but it is likely that at least some patients diagnosed as having delusional disorder will develop schizophrenia or mood disorders. Hence, current clinical criteria have limitations and need improvement, possibly with the use of laboratory techniques or more specified clinical definitions. Furthermore, the data suggest that delusional disorder is relatively chronic and is probably biologically distinct from other psychotic disorders.

THEORIES OF DELUSION FORMATION While a clear understanding of the pathogenesis of delusions remains an unfulfilled hope, several major theories have been advanced. Any adequate hypothesis for delusion formation must deal with certain facts: (1) delusions occur in a variety of medical and psychiatric diseases; (2) not all persons with such conditions develop delusions; (3) the content of delusions constitutes a relatively short list of types and is strikingly repetitious despite the variety of diseases; (4) delusions can clear rapidly with treatment of the underlying condition or its termination; (5) delusions can persist, and even become systematized; (6) delusions often accompany perceptual changes such as hallucinations or impaired sensory input; (7) delusions may be highly encapsulated features in persons such that their functioning may not be compromised socially, intellectually, or emotionally. Further, any adequate hypothesis must respond to two questions. First, why does the patient have a delusion? This is a question concerning the form of the psychopathology. Second, why does the patient have this particular delusion? This is a question concerning the content of the psychopathology.

There are three categories of theory in delusion formation.

1. Delusions arise in an otherwise intact cognitive system because a deviant pattern of motivational interest is present (psychodynamic mechanism, social attribution theory).
2. Delusions arise as the result of a fundamental cognitive defect that impairs the patient's capacity to draw valid conclusions from evidence (disorder of reasoning).
3. Delusions arise from normal cognitive processes directed at explaining abnormal perceptual experiences (psychobiological mechanism, anomalous experience hypothesis).

These theories need not be mutually exclusive. It is probable that delusional beliefs are the result of different processes involving one or more of the proposed mechanisms.

Psychodynamic mechanism In 1911 Freud published "Psychoanalytic Notes Upon an Autobiographical Account of a Case of Paranoia (Dementia Paranoides)." His interpretation of this case, which became the foundation of the psychodynamic theory of paranoia, was based on his reading of the memoirs of the presiding judge of a Dresden appeals court, Daniel Paul Schreber, who had suffered episodes of psychiatric illness in 1884, in 1885, and in 1893. The second episode led to two prolonged hospitalizations from which the patient obtained discharge in 1902 following legal action, although he was still delusional. Freud asserted that Schreber's 1903 account, *Memoirs of My Nervous Illness,* offered a legitimate basis for theory, as "paranoiacs cannot be compelled to overcome their internal resistances, and . . . in any case they only say what they choose to say. . . ." Freud argued that the written case report can take the place of personal acquaintance; and in the case of Schreber, Freud never saw the patient. Freud asserted that Schreber's case illustrated a general mechanism of delusion formation involving denial or contradiction and projection of repressed homosexual impulses that break out from the unconscious. The forms of delusion in paranoia can be represented as contradictions of the proposition "I (a man) love him (a man)." The following examples illustrate the forms of illogic.

1. Delusion of persecution. In the contradiction "I do not love him, I hate him," a hatred that persons deem unacceptable at the conscious level is transformed and becomes, instead, "He hates (elaborated to persecutes) me." Patients can then rationalize their anger by consciously hating those persons whom they perceive to hate them.
2. Delusion of erotomania. The proposition "I do not love him—I love her" is transformed through projection to "She loves me—and so I love her."
3. Delusional jealousy. To protect against unwarranted, threatening impulses, the patient transforms the proposition in this manner: "I do not love him—she (a wife, lover) loves him." Hence, jealous delusions represent the transformed attractions of the deluded for the lover.
4. Delusion of grandiosity (megalomania). Here the contradiction made is, "I do not love him—I love myself."

The essence of the theory is that delusions represent attempts to manage the stirrings of unconscious homosexuality. The dynamics of unconscious homosexuality are similar for female as well as male patients in the classic theory.

COMMENT Many theorists have added to the psychodynamical lore on delusion formation from the standpoint of understanding personality factors. For example, some of the vulnerability to delusion formation may be related to deficiently developed trust, to narcissistic dynamics, or to exaggerated traits such as hypersensitivity.

CRITIQUE Freud's mechanism of delusions sidesteps the distinction between form and content in psychopathology. He proposes an inferential process to account for the particular delusion but does not clearly address the issue of why a delusion is formed rather than another symptom, such as hallucination. Verification of the hypothesized mechanism clearly rests on finding evidence that delusions are associated with indications of homosexual tendencies. The theory has been perpetuated in part because an absence of homosexuality can never be proved, and such tendencies can be used as a pillar, even if not a scientifically or empirically demonstrable pillar, in the psychodynamic argument. The few experimental attempts made to test the hypothesis have been inconclusive or equivocal. Moreover, though homosexual concerns have been found among some delusional patients, the variety of conditions with such delusions argues against a common mechanism of unconscious homosexuality in all. Indeed those persons who delusional patients say are persecuting them are not always known by them. Neither is the persistence of such delusions adequately

accounted for in that formulation. Nevertheless, the classic approach has had immense influence and has provided important psychoanalytical concepts, such as projection, and an awareness that developmental experiences may operate to influence the content of delusional thinking. Systematic empirical study would be valuable.

Disordered reasoning Related to the psychodynamic formulation is the proposal that delusions arise on the basis of defects in formal logical reasoning. Popular in the 1950s and 1960s, this view, promulgated by Eilhard Von Domarus among others, suggested that errors in logic such as the principle of identity (two subjects are identical on the grounds of identical predicates) have an etiological role. For example, "Charles Manson used drugs; I use drugs; therefore, I am Charles Manson." The empirical assessment of that proposal has failed to establish that deluded patients exhibit more defects in reasoning; rather it appears that normal and deluded persons both make similar and frequent errors of reasoning.

Two other proposals involving disturbance in reasoning have been studied recently. The first portrays the difficulty underlying delusion formation as a failure in the application of Bayesian reasoning. According to this model of developing beliefs, making choices, and drawing conclusions, deluded patients accept conclusions at levels of probability too low for acceptance by nondelusional persons. However, attempts to demonstrate that failure have had equivocal results. The second proposal suggests that the reasoning processes of deluded patients are influenced by the person's tendency to assign meaning in a biased manner. The bias arises in making judgments about a person's behavior that assigns causes of the behavior to characteristics of the person concerned regardless of the social situation or circumstances involved. That model, based on social attribution theory, has been tested, but the results do not provide strong support for this formulation.

Other psychological mechanisms In *Manic Depressive Insanity and Paranoia,* Kraepelin considered the delusions of paranoia to be the "morbidly transformed expression of the natural emotions of the human heart" and, more specifically, "a kind of psychological compensation for the disappointments of life." He dismissed the Freudian psychodynamic mechanism on the grounds that it did not refer to a clear concept of paranoia and that it was not supported by evidence. He also emphasized constitutional factors in his formulation, including, especially, disturbances of judgment. Other authors have made similar suggestions about the role of need fulfillment in the development of paranoia. For example, delusions of persecution might serve to maintain the self-esteem of the deluded person, according to a social attribution view about delusion formation in which a normal bias—that of assigning blame for negative outcomes to other persons or circumstances—is exaggerated.

CRITIQUE Those contributions also fail to address the issue of pathogenesis rigorously. They help one to reach an understanding of the delusion, especially its content, but fail to provide an explanation of its form. The commonness of the risk factors or antecedent features cited repeatedly as central to delusion formation contrasts dramatically with the uncommonness of delusional disorder.

Psychobiological mechanism The French psychiatrist Gaëtan G. de Clerambault proposed in 1942 that chronic delusions resulted from abnormal neurological events. Infections, lesions, intoxication, and other forms of damage produce automatisms that puzzle or distress the patient initially, and eventually demand explanation. The explanations take the form of delusions. Automatisms include hallucinations, a constant parade of memories, feelings of familiarity, false recognition, arresting of thought, disturbances in attention, bizarre tactile sensations, and even kinesthetic sensation.

The view that delusions offer an explanation for hallucinations is an old concept in psychiatry that has not been well formulated. The fact that hallucinations have been introduced into and retracted from the definition of paranoia over the years also reflects a lack of clarity regarding a possible connection between the two forms of psychopathology.

Brendan Maher has proposed a similar hypothesis that conceptualizes delusions as explanations of anomalous experiences that arise in the environment, the peripheral sensory system, or the central nervous system. A central tenet of his view is that the processes whereby delusional beliefs are formed are similar in their essential nature to those that operate in the formation of normal beliefs and scientific hypotheses. Integral to the hypothesis is the assumption that components of this normal operational sequence have a neural substrate. The neural substrate may be activated either by sensory input (as in hallucinatory effects of drugs) or by the effects of brain damage (as in alcoholism). The activation of any part of the sequence demands explanation and may thus give rise to delusions. The sequence, activated by disturbances in sensory experience, emotional incongruity, or central nervous system abnormalities, has the following stages: (1) anomalous experience, (2) feelings of significance, (3) testing for reality of experience, (4) developing tentative hypothoses, (5) additional observation, (6) exploring insights, and (7) confirmation of the insight by selective observation.

In Maher's explanation, the patient is delusional because he or she actually experiences anomalies that demand explanation. The particular content of the delusion is drawn from the past or current circumstances, experience, and personal and cultural background of the patient. The explanation answers questions such as the following: What is happening? Why? Why do other people deny it is happening? Why is it only happening to me? Who is responsible for it? The delusional explanation offers relief from puzzlement, and that relief works against abandonment of the explanation.

CRITIQUE Although the psychobiological formulation has gone largely unstudied, there is supporting evidence. Studies of altered perception among patients and healthy controls experiencing sensory impairment or sensory deprivation, and among persons taking various drugs of abuse have demonstrated a high incidence of delusion formation. The failure to detect a fundamental defect in the cognitive process of delusional patients or to identify basic differences in belief formation between persons with delusions and normal controls provides indirect support as well. Clearly, this hypothesis warrants further examination, and it remains to be seen how applicable it is to conditions, such as delusional disorder, where the occurrence of hallucinations is debated. Sensory impairment and central nervous dysfunction, though apparently likely, have not been established for the disorder.

While the anomalous experience hypothesis focuses on the psychological mechanisms underlying delusion formation, a complementary proposal concerns the anatomic loci associated with delusional thinking. Jeffrey Cummings and others have used the growing data on psychopathological consequences of

neurological disease to suggest that delusions occur in diseases involving the limbic system—in particular, temporal lobe structures and caudate nuclei. Diseases characterized by excessive dopaminergic activity or reduced cholinergic activity also carry a heightened risk of delusion formation. Cummings further hypothesizes that the common locus of delusion formation is limbic dysfunction that leads to misinterpretation of the environment accompanied by inappropriate perception of threat. Both disease- and patient-related factors influence the content, complexity, and timing of the delusion.

Other relevant factors Delusions have been linked to a variety of additional factors such as social and sensory isolation, socioeconomic deprivation, and personality disturbance. The deaf, the visually impaired, and possibly immigrant groups with limited ability in a new language may be more vulnerable to delusion formation than the normal population. Vulnerability is heightened with advanced age. Delusional disturbance and other paranoid features are common in the elderly. In short, multiple factors are associated with the formation of delusions, and the source and pathogenesis of delusional disorders has yet to be specified.

DIAGNOSIS AND CLINICAL FEATURES

DELUSIONAL DISORDER

CLINICAL PRESENTATION DSM-IV defines the core psychopathological feature of delusional disorder as persistent, nonbizarre delusions not explained by other psychotic disorders (Table 15.2-2). Onset can be acute, following a precipitating event, or the disorder may emerge gradually and may become chronic. Behavioral and emotional responses are generally appropriate; neither a mood disorder nor the volitional, thinking, and emotional disturbances of schizophrenia are present. In general, patients with delusional disorder show little disorganization or impairment in their behavior or in the clarity of their thinking.

The delusions are unusual yet they refer to aspects of life that might occur, such as being conspired against, cheated on, physically ill, in love, jealous, and the like. They are, as Winokur has suggested, "possible," rather than totally incredible and bizarre as are many of the delusions of schizophrenia. The types of delusions are specified according to their content; the most common concern persecution and jealousy. The delusions are fixed (persistent) and unarguable. Patients interpret facts to fit the delusion rather than modifying the delusion to fit the facts. There is systematization in the delusional thinking, meaning that a single theme or series of connected themes is present with links to the predominant delusion.

Many have proposed that there is a descriptive continuum between paranoid personality disorder, delusional disorder, and the paranoid subtype of schizophrenia in terms of degrees of disorganization and impairment. However, there is little evidence to support the concept that these disorders share more than overlapping psychopathology.

The presence of hallucinations in delusional disorder has been debated, some arguing that schizophrenia is a more likely diagnosis in such cases, others are not so concerned as long as the hallucinations are not marked and persistent. The resolution of this issue remains distant, but it is reasonable to consider infrequent hallucinations that are not a prominent part of the psychopathology to be a feature of delusional disorder. The hallucinations are usually auditory but may be visual and tend to be more common in acute cases. Other types of hallucinations are possible; however, tactile or olfactory hallucinations may be present and even prominent if they are related to the delusional theme.

The person's emotional contact and behavior are generally intact. The emotional response is usually consistent with the delusional concern, and the mood is often appropriately depressed. Restlessness and agitation may be present. Loquaciousness and circumstantiality, usually accompanying descriptions of the delusions, are found in some patients, but formal thought disorder as sometimes found in schizophrenia is absent. Persons with delusional disorder may behave in a remarkably normal way much of the time; they become strikingly different when the delusion is focused on, at which time thinking, attitude, and mood may change direction abruptly. Social and marital functioning are more likely to be compromised than intellectual and occupational functioning.

Associated features in delusional disorder include those of the paranoid syndrome (Table 15.2-5). The degree of hostility and suspiciousness may be such that violent or aggressive behavior results. Litigious behavior is common among such patients. However, some patients, notably those with somatic delusions, may not display hostility, anger, or even suspiciousness to any considerable degree.

DIAGNOSIS Making the diagnosis of delusional disorders requires that the clinician match the features of the case to the appropriate criteria. When the clinician has successfully ruled out other disorders, certain features of the case can help substantiate the diagnosis of delusional disorder.

MENTAL STATUS EXAMINATION The patient's complaints are brought to the attention of the clinician by the patient or a third party, such as police, family, neighbors, or a consulted physician or attorney. The patient may have acted to draw attention by asking for protection, quarreling with neighbors, visiting too many clinics, or similar behavior. The complaint focuses on the distressing behavior and possibly on incidental symptoms. The patient will not complain of a psychiatric condition; in fact, he or she will deny that or the presence of any psychiatric symptoms. Examination of the patient leads to the discovery (often to the surprise of those expecting to observe a range of mental deviances) that thinking, orientation, affect, attention, memory, perception, and personality are intact. The patient's thinking is so clear and the delusional features are so central to his or her concerns that the clinician begins to anticipate precisely the responses of the patient to the point that accurate predictions of specific actions and reactions are possible. Such predictability may distinguish the behavior of the delusional disorder patient from that associated with other psychotic conditions. The patient's behavior and responses to the interview are consistent with the range of features in other paranoid conditions. There may be hostility, anger, lack of cooperation, and a sarcastic or challenging quality to most of what the patient says.

The capacity to act in response to delusions is an important dimension of the evaluation. Level of impulsiveness should be assessed and related to any potential for violence or suicidal behavior. The patient's self-righteousness, the intensity of the delusional experience, and its emotional impact on the patient may be clues to possible violent behavior; and any plans for harming others, including homicide, should be inquired about. Jealousy and erotomania are perhaps especially important concerns in the assessment of possible aggression and violence. If

such thoughts exist, the patient should be asked how they were handled in the past. Careful judgment and diplomatic interviewing are especially important in such presentations.

ASSESSMENT OF DELUSIONS The detection of delusions solidifies the judgment that a paranoid condition is present. Delusions are usually easy to detect. Features of behavior (Table 15.2-5) may suggest their presence. Associated psychopathological symptoms such as hallucinations, disturbed form of thought, and mood disorder may also provide clues that delusions are part of the clinical picture.

The clinical challenge is clear in subtle cases. Fundamentally, the clinician must make a judgment based on available observations and the reported private mental experience of the patient. Attempts to dissuade the patient with counterevidence and counterarguments may be useful in determining whether the patient's beliefs can be influenced with evidence usually sufficient to alter the belief of a nondelusional person. Spending time in discussion with the patient to grasp the nature of delusional thinking in terms of its themes, impact on the patient's life, complexity, systematization, and related features may be crucial in making the judgment. The most sensible guideline for all cases of suspected delusional thinking is to establish as comprehensive a picture as possible concerning the condition of the patient, including the patient's subjective private experience and evidence of psychopathological symptoms. Such information should reduce much of the uncertainty in the evaluative process.

Persecutory type The delusion of persecution is a classic symptom of delusional disorder. Persecutory type and jealousy type delusions are probably the forms seen most frequently by psychiatrists. In contrast to persecutory delusions in schizophrenia, the clarity, logic, and systematic elaboration of the persecutory theme in delusional disorder leave a remarkable stamp on this condition. The absence of other psychopathology, of deterioration in personality, or of deterioration in most areas of functioning also contrast with manifestations of schizophrenia.

A 29-year-old single, white man with a college background had been drifting from one clerical position to another. For years he had been convinced that a close relative was trying to get rid of him to take over the family business. He based his conviction on various remarks, coincidences, and "putting two plus two together." He appeared at a friend's apartment in an acutely agitated, fearful, and demoralized state. After trying to reassure him, the friend brought the patient to the psychiatric emergency room. The patient had made an anonymous phone call one week before to the police informing them that he had once mailed a postcard that contained a vague threat to the relative intending to scare him. Worry that advanced technologies would enable the police to trace the phone call to him had so distressed the patient that he had become preoccupied and constantly apprehensive. For several days he had been unable to sleep. However, there was no evidence of hallucinations, thought disorder, or other emotional change. The patient was reluctant to return for a follow-up visit to discuss his adjustment; he refused all medication, nor did he appear reassured by discussion of his guilt and the likelihood that the matter was not of interest to the police. He left the emergency room less agitated, however. Five years later, the patient requested consultation to discuss his preoccupation that the police were likely to determine the source of the phone call and were about to discover him. His level of functioning had not changed dramatically. He continued to have the same concerns and said he was troubled only from time to time by the worry that his cousin would contact the police. But when such thoughts did occur, he was made miserable. During those episodes of intense concern about the delusion, he was able to work but would find himself constantly distracted from his duties. It was under those circumstances that he sought out further professional attention.

Jealous type Delusional disorder with delusions of infidelity has been called conjugal paranoia when it is limited to the delusion that a spouse has been unfaithful. The eponym "Othello syndrome" has been used for the condition. The delusion usually afflicts men, often those with no prior psychiatric illness. It may appear suddenly and serve to explain a host of present and past events involving the spouse's behavior. The condition is difficult to treat and may diminish only on separation, divorce, or death of the spouse.

Richard Krafft-Ebing described the symptom of delusional jealousy in alcoholics in 1891 and believed that extreme jealousy was pathognomonic for alcoholism. Other disorders with this symptom were later described. A recent retrospective analysis of 8,134 psychiatric inpatients disclosed a prevalence of delusional jealousy of 1.1 percent among the major diagnostic groups. Among paranoid disorders (ICD-9 classification) a 6.7 percent prevalence was determined. Delusional disorder with alcohol dependence frequently shows the single delusion of jealousy, a persistent feature that sometimes remits if alcohol abuse is brought under control. In personality disorders the symptom may be confused with extreme jealousy, but other psychotic features should be absent. The prevalence of delusional jealousy among hospitalized mood disorder patients was a surprisingly low 0.1 percent. A study of 26,000 psychiatric inpatients using DSM-III-R criteria yielded a 0.17 percent rate of delusional disorder, jealous type. Jealous delusions occur much more frequently in other disorders than in delusional disorder, which is a very uncommon condition.

Marked jealousy is thus a symptom (usually termed pathological or morbid jealousy) of many disorders—including schizophrenia (where female patients more commonly display this feature), epilepsy, mood disorders, drug abuse, and alcoholism—for which treatment is directed at the primary disorder. Jealousy is a powerful emotion; when it occurs in delusional disorder or as part of another condition it can be a potentially dangerous feature and has been associated with violence, notably both suicide and homicide. The forensic aspects of the symptom have been noted repeatedly, especially its role as a motive for murder. However, physical and verbal abuse appear more frequently than extreme actions among individuals with this symptom. Caution and care in deciding how to deal with such presentations are essential not only for diagnosis but also for safety concerns.

A 39-year-old truck driver was admitted to the hospital through efforts of the police and courts following complaints by his neighbors that he was verbally abusing his wife and physically beating her. The patient vehemently denied psychiatric illness and reported that there was no reason for him to see a psychiatrist. He claimed that he was responding to his wife's long-term secret affair with another man. He asked to speak to his lawyer and refused to cooperate in the psychiatric examination except to defend his actions. He related that he had spent a great deal of time trying to assess the nature of his wife's affair. He had hired a detective and had set up a variety of electronic video and eavesdropping devices to monitor his wife's activity over the preceding weeks in an effort to document her transgressions. The patient claimed that episodes of infidelity had begun years ago both before and after his marriage. The patient was at the hospital briefly and received a trial of antipsychotic medications. The emotional turmoil he was experiencing began to diminish. The patient became more calm, but the delusional thinking persisted. The patient was able eventually to leave the hospital, free of medication. Meanwhile, his wife had decided to divorce him. At follow-up some months later he remained convinced about her infidelity, but he admitted that it did not bother him or not quite so much.

Erotomanic type Patients with erotomania have delusions of secret lovers. Most frequently the patient is a woman, but men are also susceptible to the delusion. The patient believes that a suitor, usually more socially prominent than herself, is in love with her. The delusion becomes the central focus of the patient's existence. Onset can be acute.

Erotomania, the *psychose passionelle,* is also referred to as

de Clerambault's syndrome to emphasize its occurrence in different disorders. Besides being the key symptom in some cases of delusional disorder, it is known to occur in schizophrenia, mood disorder, and other organic disorders. There was no mention of erotomania in DSM-III; the diagnosis was atypical psychosis. DSM-III-R reinstated the condition, and it remains in DSM-IV.

Patients with erotomania frequently show certain characteristics; they are generally but not exclusively women, unattractive in appearance, with low-level employment positions, who lead withdrawn, lonely lives, with single status and limited sexual contacts. They select secret lovers with substantially contrasting features. They exhibit what has been called paradoxical conduct, the delusional phenomenon of interpreting all denials of love, no matter how clear, as secret affirmations of love. The course may be chronic, recurrent, or brief. Separation from the love object may be the only satisfactory means of intervention. Although men are less commonly afflicted by this condition than women, they may be more aggressive and possibly violent in their pursuit of love. The object of aggression may not be the loved individual but a companion or protector of the love object. The tendency toward violence among male erotomanic cases may lead initially to police rather than psychiatric contact.

A 25-year-old woman was brought to the hospital by the police at the request of the court following a complaint of harassment made against her by a local priest. The patient had seen the priest during services. Several months later she had developed a passionate love for him which she was convinced he had for her as well. The priest had noticed that he was being followed by the patient when he left the rectory on errands. Eventually, he decided to confront her. In response she protested that she would do anything for him, and as the priest finally walked away in exasperation she concluded that his behavior was in reality an endorsement of his enduring love. She began to stand outside the rectory for long periods daily and to phone the priest at all hours. Eventually, the priest felt there was no other alternative but to turn the matter over to the police. She was arrested, and when interrogated about the purpose of her harassing behavior, disclosed her feelings. The hospital psychiatrist examined the patient and could find no evidence of perceptual disturbance, confusion, thought or emotional incongruity or other abnormalities in the patient's mental state besides intensity of emotional responses. The psychiatrist recommended further evaluation, and she was treated with antipsychotic medications. The treatment provided limited benefit, although the patient's general level of demoralization improved. On the other hand, the patient continued to contact the priest from the inpatient unit of the hospital by calling on the public telephone in the corridor until she was finally restricted from telephone use. There ensued a period when the patient was writing letters secretly to the priest. The patient's harassing behavior finally abated so that she could be released. She was warned that she should not approach the priest in the future. She seemed to have some understanding of the nature of the situation and said that she would abide by this recommendation. Several months later the patient was arrested again for trespassing at the priest's rectory.

Somatic type Delusional disorder with hypochondriacal delusions has been called monosymptomatic hypochondriacal psychosis. The condition differs from others with hypochondriacal symptoms in degree of reality impairment. In delusional disorder, the delusion is fixed, unarguable, and presented intensely, because the patient is totally convinced of the physical nature of the disorder. In contrast, hypochondriacs are often aware that their fear of illness is groundless. The content of the delusion may vary widely from case to case. Munro has described the largest series of cases and has used the content of delusions to define three main groups of patients: (1) those with delusions of infestation (including parasitosis); (2) those with delusions of dysmorphophobia, such as of misshapenness, personal ugliness, or exaggerated size of body parts; and (3) those with delusions of foul body odors and/or halitotis.

The frequency of these conditions is low, but they may be underdiagnosed, as patients present to dermatologists, plastic surgeons, and infectious disease specialists more often than to psychiatrists in the unremitting search for curative treatment. That feature may partially account for Kraepelin's skepticism about the occurrence of this form of paranoia. Several recent reports indicate that pimozide (a diphenylbutylipéridine and highly specific dopamine blocker) and certain serotonin-specific reuptake inhibitors may be effective in treatment of such disorders, even in cases with a variety of delusional themes. There may be a heightened association of shared psychotic disorder involving primary cases of hypochondriacal delusion. One series reported a quarter of cases with such an association.

This condition has a poor prognosis without treatment. It affects both sexes roughly equally. A previous history or family history of psychotic disorder is uncommon. In younger patients, a history of substance abuse or head injury is frequent. Although anger and hostility are commonplace, shame, depression, and avoidant behavior are even more characteristic. Suicide, apparently motivated by anguish, is not uncommon.

A 43-year-old married woman with no children was admitted with a presenting complaint of acute agitation associated with blindness. Her vision and eyes had been examined repeatedly at the local emergency room. Because she refused to accept the clinical judgment that there was no evidence of pathology, she was finally referred to the psychiatric clinic. The patient appeared to have no difficulty seeing but regarded herself to be blind and in need of various aids to manage this disability. At the hospital the patient's behavior was remarkably litigious: she demanded her own room in the hospital; she requested further eye examinations; and she indicated that she would follow only certain rules in her hospitalization. While she did complain about the blindness, it often appeared that the main concern was being able to complain and to complain to the appropriate authorities. The patient wrote a series of letters to the police, judges, and federal and state authorities urging all to become involved in her case to help in her release from an unjustified hospitalization. The patient was treated with a variety of antipsychotic and antidepressant agents with no success. She said she preferred to be without medication (claiming that she was not mentally ill). After supportive counseling and several months of hospitalization she was discharged from the hospital in fair condition, still acting as if she were blind. Months later, the patient, still apparently unable to see, was involved in a political campaign on behalf of a major presidential candidate. She had created enough difficulty in the campaign headquarters to arouse the concern of the campaign manager for the election committee. She sought no further psychiatric intervention.

Grandiose type Delusions of grandeur (megalomania) have been noted for years. They were described in Kraepelin's paranoia and have been associated with conditions fitting the description of delusional disorder.

A 51-year-old man was arrested for disturbing the peace. Police had been called to a local park to stop him from carving his initials and those of a recently formed religious cult into various stately trees surrounding a pond in the park. Confronted, he had scornfully argued that, having been chosen to begin a new townwide religious revival, it was necessary for him to publicize his intent in a permanent fashion. The police were unsuccessful at preventing the man from cutting another tree and made the arrest. Psychiatric examination was ordered at the state hospital, and the patient was observed there for several weeks. He denied any emotional difficulty and had never received psychiatric treatment. There was no history of euphoria or mood swings. The patient was angry about being hospitalized and only gradually permitted the doctor to interview him. In a few days, however, he was busy preaching to his fellow patients and letting them know that he had been given a special mandate from God to bring in new converts through his ability to heal. Eventually, the preoccupation with special powers diminished. No other evidence of psychopathology was observed. The patient was discharged, having received no medication at all. Two months later he was arrested at a local theater, this time for disrupting the showing of a film that depicted subjects he believed to be satanic.

Mixed type The category of mixed type applies to patients with two or more delusional themes. However, the diagnosis of mixed type should be reserved for cases in which no single delusional type predominates.

Unspecified type The category of unspecified type is reserved for cases in which the predominant delusion cannot be subtyped in the previous categories. An example is certain delusions of misidentification—for example, Capgras's syndrome, named after the French psychiatrist who described the *illusion des sosies* or the illusion of doubles. The delusion in Capgras's syndrome is the belief that imposters have replaced a familiar person or persons. Others have described variants of the Capgras's syndrome, namely the delusion that persecutors or familiar persons could assume the guise of strangers (Fregoli's delusion) and the very rare delusion that familiar persons could change themselves into other persons at will (intermetamorphosis) have also been described. Each disorder is not only rare but is highly associated with schizophrenia, dementia, epilepsy, and other organic disorders. Reported cases have been predominantly in women, have had associated paranoid features, and have included feelings of depersonalization or derealization. The delusion may be short-lived, recurrent, or persistent. It is unclear whether delusional disorder can appear with such a delusion. Certainly, the Fregoli and intermetamorphosis delusions have bizarre content and are unlikely; but the delusion in Capgras's syndrome is a possible candidate. The role of hallucination or perceptual disturbance in this condition needs to be explicated.

SHARED PSYCHOTIC DISORDER Shared psychotic disorder (also referred to as shared paranoid disorder, induced psychotic disorder, *folie à deux*, and double insanity) was first described by Lasegue and Falret in 1877. It is probably rare, but incidence and prevalence figures are lacking, as the literature consists almost entirely of single case reports. The disorder is characterized by the transfer of delusions from one person to another; both persons have been closely associated for a long time and typically live together in relative social isolation. In its most common form, *folie imposée* (which is covered by the DSM-IV criteria), the individual who first has the delusion (the primary case) is often chronically ill and typically is the influential member of a close relationship with a more suggestible person (the secondary case) who also develops the delusion. The secondary case is frequently less intelligent, more gullible, more passive, or more lacking in self-esteem than the primary case. If the pair separates, the secondary case may abandon the delusion, but that outcome is not uniformly seen. The occurrence of the delusion is attributed to the strong influence of the more dominant member. Old age, low intelligence, sensory impairment, cerebrovascular disease, and alcohol abuse are among the factors associated with this peculiar form of psychotic disorder. A genetic predisposition to idiopathic psychoses has also been suggested as a possible risk factor.

Other special forms have been reported, such as *folie simultanée*, where two people become psychotic simultaneously and share the same delusion. Occasionally, more than two individuals are involved (for example, *folie à trois, quatre, cinq;* also *folie à famille*), but those cases are especially rare. The most common relationships in *folie à deux* are sister-sister, husband-wife, and mother-child, but other combinations have also been described. Almost all cases involve members of a single family.

There is some question whether patients with such conditions are truly delusional rather than highly impressionable, as frequently there is merely passive acceptance of the delusional beliefs of the more dominant person (primary case) in the relationship until they are separated, at which point the unusual belief may remit spontaneously. In the DSM-IV criteria the requirement that the secondary case not have a psychotic disorder prior to onset of the induced delusion illustrates the relevance of this question. The psychopathology of secondary cases in fact varies. In DSM-III such patients were required to meet the criteria for paranoid disorder (that is, show evidence of disturbed personality and perhaps evidence of other psychiatric disorder, mental subnormality, or dementia). Probably, some cases will fit the definition of delusional disorder.

A 40-year-old woman consulted physicians to help cure her problem of disagreeable body odor. The physicians failed to satisfy the woman's hopes of diagnosis and treatment, because they found nothing wrong with her. They did occasionally recommend psychiatric consultation, which she refused. Her husband, a quiet, retiring man of 35, accompanied his wife to all medical specialist consultations. When questioned, he shared his wife's concerns about body odor and provided many examples of how distressing this problem had become. When he was told that there really was nothing wrong with his wife, he objected repeatedly and proclaimed that the doctors were incompetent. A psychiatrist was called to the clinic to see the couple and found consistent stories from both. The woman accepted a recommendation for hospitalization on the psychiatry-medical unit, and the husband returned home. After weeks of evaluation and treatment, the woman was discharged. The husband had stopped visiting, however, and when informed that his wife would be coming home, commented that he thought she had been cured of her problem. Three months later, however, the couple was again making rounds to different specialists.

A 52-year-old man was referred by the court for inpatient psychiatric examination, charged with disturbing the peace. He had been arrested for disrupting a trial, complaining of harassment by various judges. He had walked into a courtroom, marched to the bench, and begun to berate the probate judge. While in the hospital, he related a detailed account of conspiratorial goings-on in the local judiciary. A target of certain judges, he claimed he had been singled out for a variety of reasons for many years: he knew what was going on; he had kept records of wrongdoings; and he understood the significance of the whole matter. He refused to elaborate on the specific nature of the conspiracy. He had responded to it with frequent letters to newspapers, the local bar association, and even to a Congressional subcommittee. His mental state, apart from his story and a mildly depressed mood, was entirely normal. A family interview revealed that his wife and several grown children shared the belief in a judicial conspiracy directed against the patient. There was no change in delusional thinking in the patient or the family after 10 days of observation. The patient refused follow-up treatment.

The intensity of conviction is governed by the presence of the primary case in the life of the secondary case. Protection is provided by others who share the delusion and believe in the reasonableness of the response. Munro has found that shared psychotic disorder is frequently associated with delusional disorder, somatic type.

PATHOLOGY AND LABORATORY EXAMINATION

PATHOLOGY As in most psychiatric conditions, there is no evidence of localized brain pathology to correlate with clinical psychopathology. Patients with delusional disorder seldom die early and show no consistent abnormalities on neurological examination. Delusions can complicate many disorders and virtually all brain disorders. Certain disorders produce delusions at rates greater then the expected in the general population; for example, in patients with epilepsy (especially involving temporal lobe), degenerative dementias (Alzheimer's and vascular dementias), cerebrovascular disease, extrapyramidal disorders, and traumatic brain injury.

While many types of delusions have been reported in patients with brain disorders, there appear to be particular connections between delusion phenomenology and certain kinds of brain dysfunction. For example, patients with more severe cortical impairment tend to experience more simple, transient, persecutory delusions. This type of delusional experience is characteristic of conditions such as Alzheimer's multiinfarct dementia, and metabolic encephalopathy. Those disorders are also associated with significant cognitive disturbance. More com-

plex (that is, elaborate and systematic) delusional experiences tend to be more chronic, intensely held, resistant to treatment, and associated with neurological conditions producing less intellectual impairment and strong affective components. Those features occur in patients with neurological lesions involving the limbic system or subcortical nuclei rather than cortical areas. That, coupled with the observation of response of some patients to drug treatment, such as pimozide and other medications, provides a rational basis on which to hypothesize the presence of subcortical pathology, possibly involving systems subserving temporolimbic areas.

Although investigators are far from a neuropathology of delusional disorders, the available evidence suggests that if there is such a finding it will be subtle. Nevertheless, future empirical studies, guided by etiological hypotheses, could lead to breakthroughs. Given the uncommoness of delusional disorder, intensive studies of specific cases and of conditions with delusions from known causes (and with identifiable neuropathologies) offer useful beginning points.

LABORATORY EXAMINATION A range of assessments is often necessary, but several have a high likelihood of detecting key factors in the case. The use of drug screening measures is particularly valuable given the marked delusional responses induced by a number of substances, especially alcohol, amphetamine, cocaine, and other central nervous system stimulants.

Neuropsychological assessment may help disclose evidence of impaired intellectual functioning that suggests brain abnormalities. The assessment of intelligence may show discrepancies between verbal and performance scores as well as scatter in overall performance. Limited data on delusional disorder (especially the more chronic forms) suggest that average or marginally low intelligence is characteristic. Projective testing such as the Rorschach has limited value in making the diagnosis but may confirm features consistent with it. The Minnesota Multiphasic Personality Inventory (MMPI) has among its clinical scales the paranoia (Pa) scale, developed to identify paranoid symptoms. Deviation on this scale has strong correlations to paranoid features and may help substantiate the diagnosis or raise it as a possibility.

DIFFERENTIAL DIAGNOSIS

DELUSIONAL DISORDER Because delusional disorders are uncommon, idiopathic, and possess features characteristic of the full range of paranoid illnesses, differential diagnosis has a clear-cut logic: namely, delusional disorder is a diagnosis of exclusion. There are many conditions to consider (Table 15.2-10). To avoid premature diagnosis, a comprehensive strategy of careful evaluation is required.

This clinical assessment of paranoid features requires three steps. Initially, the clinician must recognize, characterize, and judge as pathologic the presence of paranoid features. Next, the clinician should determine whether they form a part of a syndrome or are isolated. Finally, the clinician should develop a differential diagnosis.

The first of the three steps must be pursued systematically. The clinician must be aware that a range of objective traits or behaviors (Table 15.2-5) is often found in paranoid illness and may constitute the only clue that a paranoid illness is present. Paranoid patients are frequently unwilling to reveal their subjective experiences to examiners or to cooperate in the clinical investigation. Careful interviewing of the patient and other informants may disclose further evidence that the behavior is clearly psychopathologic; in other cases, however, that conclusion must await further observations. Sometimes the plausibility of the delusion requires investigating to determine whether the belief is indeed delusional or not. Premature acceptance that the patient is deluded has at times been an embarrassment to some clinicians who learn that the patient was not deluded. If the judgment that the patient is delusional seems unassailable, then careful elaboration of the nature of the delusion is called for. The delusional thinking should be examined for its fixity, logic, encapsulation, degree of systematization and elaboration, and its effect on action and planning.

Having determined that a paranoid condition is present, the clinician should attend to the premorbid characteristics, the course, and associated symptoms to detect patterns of psychopathology. The discovery of clouded consciousness, perceptual disturbance, other psychopathology, physical signs, or confusing symptoms may suggest different causes for paranoid features. Isolated acute paranoid symptoms, on the other hand, often appear early in medical illness.

Finally, the clinician should avoid the temptation to make the diagnosis of schizophrenia and delusional disorder prematurely in cases where paranoid features are present, as those features occur regularly in a variety of psychiatric and medical illnesses. Consequently, awareness of the multiple causes of paranoid features (step one) is essential to completing the differential diagnosis (step three).

Certain principles should guide effective assessment. First, it

TABLE 15.2-10
Differential Diagnosis of Delusional Disorder

Disorder	Delusions	Hallucinations	Awareness	Other Features
Delusional disorder	+	Occasionally	Alert	Free of psychopathology generally
Psychotic disorder due to a general medical condition, with delusions	+	+	May be impaired	Cognitive changes; substance abuse history; impairment frequent
Schizophrenia	+ (bizarre)	+	Alert	Emotional changes, pervasive thought disorder; impairment
Major depressive episode	+ (mood congruent)	+/−	Alert	Concerted changes in mood and neurovegetative features
Manic episode	+ (mood congruent)	+/−	Alert	Concerted changes in mood, need for sleep, activity, energy, lack of inhibition
Personality disorders	−	−	Alert	Not psychotic
Obsessive-compulsive disorder	−	−	Alert	Not psychotic; impairment present often
Somatoform disorders	−	−	Alert	Not psychotic
Shared psychotic disorder	+	−	Alert	Close associate has some delusions

is important to have knowledge of the paranoid features and patterns of the clinical conditions in which they occur. For example, a small percentage (10 to 20 percent) of schizophrenia cases begin after age 40, and most idiopathic psychiatric problems do not begin after age 50. Second, the premorbid status of the patient should be determined. Generally, a normal premorbid state suggests that acute paranoid features are the consequence of medical disease. Third, an abrupt change in personality, mood, ability to function, and mental state should be noted as this may indicate complications resulting from medical disease. Fourth, in those cases in which there is evidence that the patient has been refractory to psychotropic medication or psychotherapy, the continuing presence of paranoid features should alert the clinician to consider alternative diagnoses.

The final diagnosis in cases where paranoid features are prominent should be made only following: (1) a complete medical and psychiatric history with special attention to alcohol and drug history (including drugs of abuse, prescribed drugs, and over-the-counter medication history); (2) a thorough physical examination, including neurological and mental status examinations; (3) appropriate laboratory studies, particularly serological, toxicological, endocrine, microbiological, radiological, and electroencephalographic studies.

There are certain delusional conditions that, because of their frequency and seriousness, should be routinely considered in the differential diagnosis, as among the most likely sources of delusions. Delirium, dementia, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder should receive special attention.

Psychotic disorder due to a general medical condition, with delusions Delusions arise in a number of organic diseases and syndromes. Many are listed in Table 15.2-4. What they frequently have in common is a disturbance of perception particularly of visual and auditory functioning. Physical, neurological, and mental status study, and laboratory examinations, will usually enable detection of organic causes of delusions. A special focus in each evaluation should be on perceptual disturbance. Medical conditions associated with delusions should be searched for, according to the guidelines outlined concerning differential diagnosis.

Substance-induced psychotic disorder, with delusions Drug intoxications are particularly relevant. Abused drugs, such as amphetamines and cocaine; over-the-counter drugs, such as sympathomimetics; and prescribed drugs, such as steroids and L-dopa, can cause substance-induced psychotic disorder, with delusions, often without cognitive impairment. A careful drug history and screen may establish the diagnosis. A history of alcohol abuse or dependence is so common that it should always be considered. Alcoholism is often associated with jealousy, presecutory ideas, and poor impulse control.

Cognitive disorders Dementia should be considered when paranoid features occur, particularly in older persons. Mental status examination should uncover characteristic cognitive changes absent in delusional disorder. Delirium, with its fluctuating course, confusion, memory impairment, and transient delusions, contrasts with the clarity of mental functioning and the persistence of delusions in delusional disorder, and should be considered in acute cases with paranoid features.

Schizophrenia Delusions may be the presenting feature of schizophrenia. That diagnosis should be considered when the delusions are implausible or bizarre, affect is blunted or incongruous with thinking, auditory or visual hallucinations are prominent, thought disorder is pervasive, and role functioning is impaired. Paranoid schizophrenic persons may have somewhat less bizarre delusions, but role functioning is impaired, and prominent auditory hallucinations are often present, in contrast with delusional disorder.

Shared psychotic disorder The delusions and symptoms of shared psychotic disorder may resemble those of delusional disorder; but the delusions arise in the context of a close relationship with a delusional person, are identical in content to the delusions of that person, and diminish or disappear when secondary and primary case are separated.

Mood disorders with psychotic features The persistent and profound dysphoric mood of depressed patients often points to the proper diagnosis; in delusional disorder, affect may be intense, but is not itself an overwhelming or preoccupying experience to the patient. Delusions in depression, if present, are frequently related to mood (mood congruent delusions). For example, the patient with feelings of worthlessness or guilt may consider that persecution against him or her is justified as a punishment for evil ways. Somatic delusions may be puzzling to differentiate if the clinician fails to consider associated psychopathological features. If delusions occur exclusively during mood episodes, the diagnosis is mood disorder with psychotic features. Depression refers to a host of signs and symptoms, and usually has a constellation of neurovegetative features (affecting appetite, sleep, libido, energy, and so forth) that are not part of delusional disorder. Moreover, depression is frequently cyclical and is often associated with a positive family history of mood disorder. Delusional disorder, in contrast, is remarkably free of symptoms other than the delusion. Occasionally, mood symptoms that meet the criteria for a mood episode are present in a delusional condition. Delusional disorder is diagnosed only if the total duration of all mood episodes remains brief relative to the total duration of the delusional disturbance.

Manic episode Manic delusions, often grandiose and therefore mood congruent, occur in the severest stages of this illness. This could mislead the diagnostician, but the cyclical nature, the marked change in mood (often euphoric or irritable at a very intense level), the reduced need for sleep, increased energy, easy distractibility and lack of focused concentration ability, lack of social inhibition, and increased activity level of manic episodes should be decisive in distinguishing that condition from delusional disorder.

Obsessive-compulsive disorder Severe forms of this disorder should be considered in the differential diagnosis, especially obsessive-compulsive disorder with poor insight. Preoccupation with fear, unusual rituals, and obsessional beliefs may be puzzling, yet the pervasive effects of the condition on functioning differ from the experience of delusional disorder. Moreover, delusions and hallucinations should be absent. In practice, that differential may be difficult without a long period of observation.

Somatoform disorders Severe forms of body dysmorphic disorder may be difficult to distinguish from delusional disorder. The degree of conviction about imagined physical disfigurement may be the only guideline for the differential diagnosis.

Lack of other features of psychopathology, often present in such cases, may also help make the distinction.

Hypochondriasis may also be distinguished on the basis of absence of delusions, although many of the behaviors associated with delusional disorders, somatic type, may occur. Usually such patients reveal some doubt or uncertainty about the validity of their health preoccupations. Their overvalued beliefs about disease or affliction may clearly resemble delusional disorder, somatic type; severe cases may require considerable diagnostic effort.

Paranoid personality disorder Individuals with paranoid personality disorder by definition have abundant paranoid features. They are persistently oversensitive, ready to take offense, suspicious, resentful, rigid, and frequently self-centered. Rather than delusions, such persons tend to have strongly held ideas (overvalued ideas). Generally, however, they are believed to be free of delusions. This is the most useful differential feature. There is some evidence that this personality pattern occurs often enough in families of probands with delusional disorder to suggest a possible genetic connection between the two. This relationship remains unclear at present.

Schizoid personality disorder and schizotypal personality disorder Paranoid features may occur in these personality disorders as well. The pervasive disturbance in personality functioning and the absence of delusions and other psychotic features are usually definitive distinguishing characteristics.

Disorders of aging Any discussion of differential diagnosis of paranoid features is incomplete unless consideration is given to the occurrence of paranoid features in the elderly. Paranoid features develop frequently in the elderly, and assessment in such cases should be particularly thorough. Our understanding of paranoid features among the aged is limited. There are several facts worth knowing: (1) the association of depressive illness with paranoid features is high enough to warrant suspicion of mood disorder in all cases with paranoid features; (2) there appears to be a late-occurring form of schizophrenia sometimes labeled late paraphrenia or late-onset schizophrenia in which paranoid characteristics frequently occur (this controversial diagnosis, however, would be warranted only when no other disorders could be diagnosed); (3) the sudden onset of acute paranoid features in the elderly can be a sign of cerebrovascular injury or other medical illness; (4) many of the medical conditions associated with delusions have increased incidence in the elderly population; (5) perhaps most important for the general clinician is to recognize sources of increased risk of paranoid disorder among older individuals. It is now known that many factors contribute to the incidence of paranoid features in the aged, including lack of stimulating company, isolation, physical illness, the aging process itself, loss of hearing, and loss of visual acuity, each of which should be carefully assessed. Delusional disorder may be present in the elderly, may even have its onset in the elderly, but the frequency of other causes of paranoid features calls for a prudent, systematic search.

SHARED PSYCHOTIC DISORDER Malingering, factitious disorder with predominantly psychological signs and symptoms, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder need to be considered in the differential diagnosis of shared psychotic disorder. The boundary between shared psychotic disorder and generic group madness, such as the Jonestown massacre in Guyana, is unclear.

COURSE AND PROGNOSIS

DELUSIONAL DISORDER Onset can begin in adolescence but generally occurs from middle to late adulthood on with variable patterns of course, including lifelong disorder in some cases. Studies generally indicate that delusional disorder does not lead to severe impairment or change in personality, but rather to a gradual, progressive involvement with the delusional concern. Suicide has been associated with such disorders, although most patients live the normal life span. The base rate of spontaneous recovery may not be as low as previously thought. Retterstol's personal follow-up investigation of a large series of cases has provided much of the viewpoint on the natural history of the disorder, but other studies have added information.

The more chronic forms of the illness (patients presenting with features for more than six months) have their onset early in the fifth decade. Onset is acute in nearly two thirds of the cases, and gradual in the remainder. In 53 percent the delusion has disappeared at follow-up study, is improved in 10 percent, and is unchanged in 31 percent. In more acute forms of the illness the age of onset is in the fourth decade, a lasting remission occurs in over half of patients, and a pattern of chronicity develops in only 10 percent. A relapsing course occurred in 37 percent.

Thus the more acute and earlier the onset, the more favorable the prognosis. The presence of precipitating factors signifies a positive outcome, as does being a woman and married. In terms of prognosis, the persistence of delusional thinking is most favorable for cases with persecutory delusions, and somewhat less favorable for delusions of grandeur and jealousy. Outcome in terms of overall functioning appears, however, somewhat more favorable for the jealousy subtype. Such patients may experience fewer hospitalizations and are less likely to be complicated by more severe psychotic or schizophrenic deteriorations. Work status at follow-up has indicated that the vast majority of patients are employed. These observations, though limited to few cases, provide some basis for optimism: perhaps half of cases with delusional disorders may remit, but relapse and chronicity are common.

SHARED PSYCHOTIC DISORDER The nature of the disorder suggests that separation of the submissive person who has shared psychotic disorder (the secondary case) from the dominant person (the primary case) should result in the resolution and the disappearance of the psychotic symptoms in the submissive person. Often, the submissive person requires treatment with antipsychotic drugs, just as the dominant person needs antipsychotic drugs for his or her psychotic disorder. Because the persons are almost always from the same family, they usually move back together after release from a hospital. If separated, the patient will experience a possible remission. If not separated, the patient may have a similar prognosis as the primary case.

TREATMENT

DELUSIONAL DISORDER The goals of treatment are to establish the diagnosis, to decide on appropriate interventions, and to manage complications. Fundamental to the success of those goals is an effective and therapeutic doctor-patient relationship. Establishing that is far from simple. The patients do not complain about psychiatric symptoms and often enter treat-

ment against their will. Even the psychiatrist may be brought into their delusional nets.

Psychosocial treatments There is not enough evidence to substantiate the claims for any particular school or approach in talking with the patient. Insight-oriented therapy is usually contraindicated, but a combination of supportive psychotherapeutic approaches and possibly cognitive-behavioral interventions is sensible. It is unlikely that there is any psychiatric condition that requires greater diplomacy, openness, and reliability from the therapist. Considerable skill is required in dealing with the profound and intense feelings that accompany these disorders.

Awareness of the fragile self-esteem and unusual sensitivity of these patients is essential for general management and somatic treatment. Direct questioning about the veracity of the delusion, apart from carefully establishing its nature and the evidence to support it during clinical evaluation, is seldom helpful. Although forging an alliance may be especially difficult, responding to the patient's concerns rather than the delusion itself may be effective. Understanding that fear and anxiety serve to stimulate hostility may be the key to adopting a flexible approach that promotes empathy but maintains physical and emotional distance. Patients with the disorder suffer. They often feel demoralized, miserable, isolated, and abandoned. They may face rejection at home or on the job. However, they can be approached, and their treatment focused on such experiences.

The goals of supportive therapy are to allay anxiety, initiate discussion of troubling experiences and consequences of the delusion, and thereby gradually to develop a collaboration with the patient. In some patients this strategy allows the psychiatrist to suggest means of coping more successfully with the delusional thinking. For example, the psychiatrist might encourage the patient to keep those ideas to oneself as they might lead to surprise, dismay, or amazement in others at considerable cost to the patient. For others, if the patient is amenable, it may be possible to provide educational intervention to help the patient understand how factors such as sensory impairment, social and physical isolation, and stress contribute to making matters worse. In all such approaches, the overriding aim is to assist in a more satisfying general adjustment.

Cognitive approaches have attempted to reduce delusional thinking through modification of the belief itself, focusing on the reasoning or the reality testing of the deluded patient. Unlike noncognitive behavioral approaches that center attention on reduction of verbal behavior (talking about the delusion), this strategy seeks a more lasting and clinically meaningful intervention through multiple techniques that keep the relationship with the patient collaborative. Those techniques include distancing, homework, and exploration of emotions associated with various delusion. The effectiveness of cognitive and behavioral therapies has not been studied enough to justify recommendation. It is important to determine the long-term as well as the short-term impact of these treatments. Nevertheless, they are promising enough to continue assessment.

Somatic treatment Delusional disorder is a psychotic disorder by definition, and the natural presumption has been that the condition would respond to antipsychotic medication. Because controlled studies are lacking and the disorder is uncommon, the results required to support this practice have not yet been obtained. Munro and others have reported beneficial responses with pimozide, in monosymptomatic hypochondriacal psychosis especially and in certain other delusional disorder subtypes. The impression remains that antipsychotic drugs are effective, and a trial especially with pimozide may be warranted. Certainly, trials of antipsychotic medication make sense when the agitation, apprehension, and anxiety that accompany delusions are prominent.

Delusional disorders respond less well generally to electroconvulsive treatment than do major mood disorders with psychotic features. According to case reports, some cases may respond to serotonin-specific reuptake inhibitors. In cases where differential diagnosis is unclear between delusional disorder and psychotic depression, a trial of combined antipsychotic and antidepressant therapy may be worthwhile. In cases where standard strategies are unsuccessful, trials of lithium or of anticonvulsant medication (for example, carbamazepine [Tegretol]) probably should be considered. However, we have no systematic information to support such approaches.

Use of somatic treatment is difficult on two levels. The patients' insistence on lack of psychiatric problems may be an insurmountable barrier to initiating treatment, and their sensitivity to all side effects may constitute an additional frustrating factor in their care. An open and clear approach to warn patients about and to assist them through possible unpleasant experiences is essential.

In general, some patients, especially younger delusional patients, respond to supportive management and somatic treatment. Unfortunately, others, especially the elderly, are refractory to attempts to reduce their delusional thinking. In all cases goals that are realistic and modest are the most sensible. As most of the difficulty in this disorder results from the effects of the patient's actions concerning the delusions, any preventive approach has considerable potential value.

Hospitalization Most delusional disorder patients can be treated effectively in outpatient settings. Hospitalization may be necessary when there is potentially dangerous behavior or unmanageable aggressiveness. The patient may show signs of poor impulse control, excessive motor and psychic tension, unremitting anger, brooding, and even threats. Suicidal ideation and planning are also potential grounds for hospitalization. Patients with erotomania, jealousy, and persecutory delusions are particularly at risk. Once the psychiatrist decides on hospitalization, it is preferable to inform the patient tactfully that voluntary hospitalization is necessary. If this strategy fails, legal means to commit the patient to a hospital must be undertaken.

SHARED PSYCHOTIC DISORDER The initial step in treatment is the separation of the affected person from the source of the delusions, the dominant partner. The patient may need significant support to compensate for the loss of that person. The patient with shared psychotic disorder should be observed for the remission of the delusional symptoms. Antipsychotic drugs can be used if the delusional symptoms have not abated in one or two weeks.

Psychotherapy with nondelusional members of the patient's family should be undertaken, and psychotherapy with both the patient with shared psychotic disorder and the dominant partner may be indicated later in the course of treatment. In addition, the mental disorder of the dominant partner should be treated.

To prevent the recurrence of the syndrome, the clinician must use family therapy and social support to modify the family dynamics and to prevent the redevelopment of the syndrome. It is often useful to make sure that the family unit is exposed to input from outside sources to decrease the family's isolation. In short, a comprehensive approach emphasizing support and, when necessary, medication is useful.

SUGGESTED CROSS-REFERENCES

Conditions to be differentiated for delusional disorders are discussed in Chapter 14 on schizophrenia, in Chapter 16 or mood disorders, in Chapter 18 on somatoform disorders, in Chapter 25 on paranoid personality disorder, in Section 17.3 on obsessive-compulsive disorder; and in Chapter 12 on mental disorders due to a general medical condition. Aging is discussed in Section 49.4, and psychiatric disorders in the elderly in Section 49.6i.

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15.3 ACUTE AND TRANSIENT PSYCHOTIC DISORDERS AND CULTURE-BOUND SYNDROMES

JUAN E. MEZZICH, M.D., Ph.D.
KEH-MING LIN, M.D., M.P.H.

INTRODUCTION

Psychotic disorders not only are severe forms of psychopathology with major implications for both clinical care and public health, but are also quite intricate and complex in their range of symptomatology, course, and context. Although schizophrenia and bipolar disorders are the major psychotic categories in the 10th revision of the World Health Organization's (WHO's) *International Classification of Diseases and Related Health Problems* (ICD-10) and the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), a number of other psychotic conditions are recognized and delineated within those classifications.

Schizoaffective disorder has been regarded for decades as the intermediate psychosis *par excellence*. More recently, several additional categories have emerged, based on acuteness and response to stress (for example, schizophreniform disorder and brief psychotic disorder). Even more recently, ICD-10 has incorporated under the umbrella of acute and transient psychotic disorders a number of multiform and relatively short-lived conditions originally described in northern European countries and in traditional societies in Asia, Africa, and Latin America. The internationally informed and conceptually flexible framework of the acute and transient psychotic disorders also render them highly relevant for the discussion of culture-bound syndromes with psychoticlike features. Those variously delineated conditions characteristically emerge or adopt distinctive forms in certain societies or cultures, indicating the need always to consider cultural factors when assessing psychiatric patients.

HISTORY

As depicted in ancient times, madness often took the form of short-lived insanity. In ancient Greek mythology, for example, Ajax experienced a brief madness when he was refused the armor of Achilles, and Agave tore her son Pentheus to pieces and then recovered. Before the 19th century clinicians tended to attribute madness either to psychosocial stressors or to somatic illnesses (particularly fevers) and mental hospitalizations were much briefer than at the end of that century.

There are two major antecedents for the current ICD-10 concept of acute and transient psychotic disorders. One encompasses a group of special psychoses identified in northern European countries. The other is the acute psychoses observed in traditional or developing countries.

ACUTE PSYCHOSES IN NORTHERN EUROPE Particularly conspicuous are the French category of *bouffée délirante*, the Scandinavian concept of psychogenic psychosis, and the cycloid psychoses described in Germany by Karl Leonhard. Those psychotic conditions have sometimes been regarded as intermediate, in the sense that they are not schizophrenic or bipolar disorders.

Bouffée délirante was only one of more than 20 terms used in 19th-century France to describe transient psychoses, reflecting protean and alternating manifestations. Frequently, the disorder starts abruptly, presenting polymorphic phenomenology (multiple and disorganized delusions, with or without hallucinations; depersonalization or derealization, with or without confusion; depression; or elation), with symptoms changing from day to day or even from hour to hour. Some cases seem to represent a response to a psychosocial stressor, whereas others do not. *Bouffée délirante* is typically transitory (with manifestations disappearing completely in a few weeks or months), but it may recur.

The concept of psychogenic psychosis was described by the Danish psychiatrist August Wimmer in 1916, building on Karl Jaspers' psychopathology background. It is a reactive psychosis that arises in immediate response to psychosocial trauma (the nature of which determines the content of the psychosis) in persons with particularly vulnerable personalities. It tends to have a benign course of a few weeks, followed by complete recovery. Studies suggest that it was diagnosed in 10 to 25 percent of all psychotic cases in Scandinavian countries. In the eighth and ninth revisions of ICD (ICD-8 and ICD-9) the use of the diagnosis was minimal.

Cycloid psychoses were one of the various types of endogenous psychoses described by Leonhard. He indicated that cycloid psychoses had a benign long-term prognosis and presented a periodic course oscillating between particular extremes, which characterized their three subtypes: anxiety-happiness, motility (hyperkinesia-hypokinesia), and excited-inhibited confusion. That complex diagnosis influenced research and clinical care in various countries, as shown by the work of Carlo Perris in Sweden, for whom its main feature was polymorphic symptomatology, and that of Kimura and Yamashita in Japan.

ACUTE PSYCHOSES IN ASIA, AFRICA, AND LATIN AMERICA There is a high prevalence of acute and transient psychoses in traditional societies and nonindustrialized countries. For example, a major multicentric study conducted by the Indian Council of Medical Research, involving over 300 persons presenting a psychotic picture that had started during the previous two weeks, found that more than 75 percent of the patients had fully recovered, with no relapse, during the course of a one-year follow-up.

Studies in sub-Saharan Africa produced acute psychotic pictures similar to those described in Asia and Latin America, with acute onset, amorphous phenomenology (excitement, disorganized behavior, confusion, affective changes, thought disturbances), and frequent precipitation by life events. Those psychoses were more common in underprivileged persons with a background of poor physical health and living in a social setting where such behavior under stress is culturally acceptable. The duration of psychosis was usually brief with or without antipsychotic medication.

A major collaborative study was recently organized by the WHO using the Schedule for Clinical Assessment of Acute Psychotic States. It entered over 1,000 cases of acute first-episode psychosis in India (where about half of all cases were seen at several centers), Denmark, Indonesia, Nigeria, the Philippines, the United Kingdom, and the United States (Hawaii). A large proportion of patients with acute psychoses had typically schizophrenic symptoms, about half showed evidence of an immediate precipitating stress, and subjects tended to be young adults of both genders from below-average socioeconomic groups. On follow-up it was observed that recovery was rapid, often within weeks, and that during the first year about two thirds of the patients had remained well, with no relapse. Those patients with schizophrenialike symptoms were as likely to have a favorable outcome as those with only affective symptoms.

Very recent analyses from the WHO Determinants of Outcome Study revealed that the incidence of nonaffective acute remitting psychotic disorders in developing countries was 10 times greater than in industrialized countries. To put that in perspective, one must remember that over 80 percent of the world population reside in developing countries.

DEFINITION AND COMPARATIVE NOSOLOGY

ICD-10 The acute psychoses described in northern European and in developing countries have been, for the first time, accommodated and organized in ICD-10, under the category of acute and transient psychotic disorders.

The conditions are formulated and arranged according to the following principles, in order of priority:

1. An acute onset (less than two weeks) as the key criterion for the whole group. Acute onset denotes a change within two weeks or less from a state without psychotic features to a clearly abnormal psychotic state (not necessarily at its peak severity).
2. The presence of typical syndromes. Those include, first, a rapidly changing and variable state, called polymorphic, prominent in acute psychoses described in several countries, and, second, the presence of typical schizophrenic symptoms.
3. The presence or absence of associated acute stress (within two weeks of the first psychotic symptoms).

Complete recovery usually occurs within one to three months (depending on the specific disorder), often within a few weeks or days. Only a small proportion of patients with those conditions develop persistently disabling states.

More details on the clinical use of acute and transient psychotic disorders can be obtained from WHO's *ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines*. Table 15.3-1exhibits the corresponding, more rigorous Diagnostic Criteria for Research for acute and transient psychotic disorders.

DSM-IV The evaluation of a psychotic patient requires the consideration of the possibility that the psychotic symptoms are the result of a general medical condition (for example, a brain tumor) or the ingestion of a substance (for example, phencyclidine).

Those two situations are classified in DSM-IV as *psychotic disorder due to a general medical condition* and *substance-induced psychotic disorder*, respectively. DSM-IV also includes a diagnosis of *catatonic disorder due to a general medical condition* to emphasize the special considerations regarding the differential diagnosis of catatonic symptoms (Chapter 12).

DSM-IV also includes psychotic disorder not otherwise specified (NOS) for psychotic disorders that do not meet the criteria for any other specific psychotic disorder. In previous editions of DSM, those were called atypical psychoses.

CULTURE-BOUND SYNDROMES A variety of culture-bound syndromes have been described in the literature. The culture-bound syndromes can often be fitted into one or another DSM-IV diagnosis, including psychotic disorder not otherwise specified. Other syndromes in addition to those discussed below are listed in Table 15.3-2.

EPIDEMIOLOGY

Relevant epidemiological data about acute and transient psychotic disorders, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder are lacking.

TABLE 15.3-1
ICD-10 Diagnostic Criteria for Research for Acute and Transient Psychotic Disorders

F23 **Acute and transient psychotic disorders**
- G1 There is acute onset of delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these. The time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed two weeks.
- G2 If transient states of perplexity, misidentification, or impairment of attention and concentration are present, they do not fulfil the criteria for organically caused clouding of consciousness as specified for F05.-, criterion A.
- G3 The disorder does not meet the symptomatic criteria for manic episode (F30.-), depressive episode (F32.-), or recurrent depressive disorder (F33.-).
- G4 There is insufficient evidence of recent psychoactive substance use to fulfil the criteria for intoxication (F1x.0), harmful use (F1x.1), dependence (F1x.2), or withdrawal states (F1x.3 and F1x.4). The continued moderate and largely unchanged use of alcohol or drugs in amounts or with the frequency to which the individual is accustomed does not necessarily rule out the use of F23; that must be decided by clinical judgment and the requirements of the research project in question.
- G5 *Most commonly used exclusion clause.* There must be no organic mental disorder (F00–F09) or serious metabolic disturbances affecting the central nervous system (not including childbirth).

A fifth character should be used to specify whether the acute onset of the disorder is associated with acute stress (occurring two weeks or less before evidence of first psychotic symptoms):
F23.x0 Without associated acute stress
F23.x1 With associated acute stress
For research purposes it is recommended that change of the disorder from a nonpsychotic to a clearly psychotic state is further specified as either abrupt (onset within 48 hours) or acute (onset in more than 48 hours but less than two weeks).

F23.0 **Acute polymorphic psychotic disorder without symptoms of schizophrenia**
- A. The general criteria for acute and transient psychotic disorders (F23) must be met.
- B. Symptoms change rapidly in both type and intensity from day to day or within the same day.
- C. Any type of either hallucinations or delusions occurs, for at least several hours, at any time from the onset of the disorder.
- D. Symptoms from at least two of the following categories occur at the same time:
  - (1) emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability;
  - (2) perplexity, or misidentification of people or places;
  - (3) increased or decreased motility, to a marked degree.
- E. If any of the symptoms listed for schizophrenia (F20.0–F20.3), criteria G(1) and (2), are present, they are present only for a minority of the time from the onset (i.e., criterion B of F23.1 is not fulfilled).
- F. The total duration of the disorder does not exceed three months.

F23.1 **Acute polymorphic psychotic disorder with symptoms of schizophrenia**
- A. Criteria A, B, C, and D of acute polymorphic psychotic disorder (F23.0) must be met.
- B. Some of the symptoms for schizophrenia (F20.0–F20.3) must have been present for the majority of the time since the onset of the disorder, although the full criteria need not be met (i.e., at least one of the symptoms in criteria G1 (1) a to G1 (2) c).
- C. The symptoms of schizophrenia in criterion B above do not persist for more than one month.

F23.2 **Acute schizophrenialike psychotic disorder**
- A. The general criteria for acute and transient psychotic disorders (F23) must be met.
- B. The criteria for schizophrenia (F20.0–F20.3) are met, with the exception of the criterion for duration.
- C. The disorder does not meet criteria B, C, and D for acute polymorphic psychotic disorder (F23.0).
- D. The total duration of the disorder does not exceed one month.

F23.3 **Other acute predominantly delusional psychotic disorders**
- A. The general criteria for acute and transient psychotic disorders (F23) must be met.
- B. Relatively stable delusions or hallucinations are present but do not fulfil the symptomatic criteria for schizophrenia (F20.0–F20.3).
- C. The disorder does not meet the criteria for acute polymorphic psychotic disorder (F23.0).
- D. The total duration of the disorder does not exceed three months.

F23.8 **Other acute and transient psychotic disorders**
Any other acute psychotic disorders that are not classifiable under any other category in F23 (such as acute psychotic states in which definite delusions or hallucinations occur but persist for only small proportions of the time) should be coded here. States of undifferentiated excitement should also be coded here if more detailed information about the patient's mental state is not available, provided that there is no evidence of an organic cause.

F23.9 **Acute and transient psychotic disorder, unspecified**

Table from World Health Organization: *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research.* World Health Organization, Geneva, 1992. Used with permission.

ETIOLOGY

CULTURAL FACTORS The diagnosis of psychotic disorders depends primarily on the accurate and thoughtful assessment of delusions, hallucinations, and bizarre psychomotor behaviors. Culture profoundly influences the meaning and nature of symptoms in all those areas, frequently leading to misdiagnosis and diagnostic ambiguity in cross-cultural clinical situations. Lacking adequate information on what constitutes normal behavior patterns or culturally sanctioned idioms of distress, clinicians evaluating patients with different cultural, ethnic, or religious backgrounds are likely to misidentify less severe complaints or behaviors as delusional, hallucinatory, or bizarre. Similarly, they are likely to suspect the existence of major psychopathology in patients with fleeting psychotic manifestations.

Spiritual and religious beliefs can present major sources of diagnostic dilemma for clinicians. Beliefs in witchcraft and sorcery are common in many societies and may or may not be delusional. Spiritism, Santeria, and various other religious movements, and different forms of shamanism practiced in many parts of the world, encourage and sanction personal communication and active involvement with the dead, with spirits, and with various deities. Such supernatural and mystical practices and experiences are not necessarily indicative of psychopathology. However, such culturally congruent beliefs often also exert substantial pathoplastic influences on symptom formation in psychotic patients. Similarly, possession and trance phenomena are frequently seen in most non-Western societies, and it is often difficult to determine whether those experiences, in a particular case, are part of an ongoing psychotic process or are culturally and contextually appropriate.

SOCIOPOLITICAL FACTORS Sociopolitical factors can also significantly influence symptom formation in psychiatric patients, thereby complicating the diagnosis of psychotic conditions. Sustained exposure to racist and discriminatory behaviors tends to increase levels of vigilance and suspiciousness among members of ethnic minorities, and it may contribute to a higher propensity for paranoid symptoms in such persons. Paranoid symptoms also are more prevalent among those, such as refugees, who are forced to live in an unfamiliar cultural milieu. Fear of political persecution is a reality of life for persons living under oppressive regimes, and it may contribute to a higher prevalence of paranoid ideation in such societies.

TABLE 15.3-2
Culture-Bound Syndromes

amok A dissociative episode characterized by a period of brooding followed by an outburst of violent, aggressive, or homicidal behavior directed at persons and objects. The episode tends to be precipitated by a perceived slight or insult and seems to be prevalent only among men. The episode is often accompanied by persecutory ideas, automatism, amnesia, exhaustion, and a return to premorbid state following the episode. Some instances of amok may occur during a brief psychotic episode or constitute the onset or an exacerbation of a chronic psychotic process. The original reports that used this term were from Malaysia. A similar behavior pattern is found in Laos, Philippines, Polynesia (*cafard* or *cathard*), Papua New Guinea, and Puerto Rico (*mal de pelea*), and among the Navajo (*iich'aa*).

ataque de nervios An idiom of distress principally reported among Latinos from the Caribbean, but recognized among many Latin American and Latin Mediterranean groups. Commonly reported symptoms include uncontrollable shouting, attacks of crying, trembling, heat in the chest rising into the head, and verbal or physical aggression. Dissociative experiences, seizurelike or fainting episodes, and suicidal gestures are prominent in some attacks but absent in others. A general feature of an ataque de nervios is a sense of being out of control. Ataques de nervios frequently occur as a direct result of a stressful event relating to the family (e.g., news of the death of a close relative, a separation or divorce from a spouse, conflicts with a spouse or children, or witnessing an accident involving a family member). Persons may experience amnesia for what occurred during the ataque de nervios, but they otherwise return rapidly to their usual level of functioning. Although descriptions of some ataques de nervios most closely fit the DSM-IV description of panic attacks, the association of most ataques with a precipitating event and the frequent absence of the hallmark symptoms of acute fear or apprehension distinguish them from panic disorder. Ataques span the range from normal expressions of distress not associated with having a mental disorder to symptom presentations associated with the diagnoses of anxiety, mood, dissociative, or somatoform disorders.

bilis and **colera** (also referred to as *muina*) The underlying cause is thought to be strongly experienced anger or rage. Anger is viewed among many Latino groups as a particularly powerful emotion that can have direct effects on the body and can exacerbate existing symptoms. The major effect of anger is to disturb core body balances (which are understood as a balance between hot and cold valences in the body and between the material and spiritual aspects of the body). Symptoms can include acute nervous tension, headache, trembling, screaming, stomach disturbances, and, in more severe cases, loss of consciousness. Chronic fatigue may result from the acute episode.

bouffée délirante A syndrome observed in West Africa and Haiti. The French term refers to a sudden outburst of agitated and aggressive behavior, marked confusion, and psychomotor excitement. It may sometimes be accompanied by visual and auditory hallucinations or paranoid ideation. The episodes may resemble an episode of brief psychotic disorder.

brain fag A term initially used in West Africa to refer to a condition experienced by high school or university students in response to the challenges of schooling. Symptoms include difficulties in concentrating, remembering, and thinking. Students often state that their brains are "fatigued." Additional somatic symptoms are usually centered around the head and neck and include pain, pressure or tightness, blurring of vision, heat, or burning. "Brain tiredness" or fatigue from "too much thinking" is an idiom of distress in many cultures, and resulting syndromes can resemble certain anxiety, depressive, and somatoform disorders.

dhat A folk diagnostic term used in India to refer to severe anxiety and hypochondriacal concerns associated with the discharge of semen, whitish discoloration of the urine, and feelings of weakness and exhaustion. Similar to *jiryan* (India), *sukra prameha* (Sri Lanka), and *shen-k'uei* (China).

falling-out or **blacking out** Episodes that occur primarily in southern United States and Caribbean groups. They are characterized by a sudden collapse, which sometimes occurs without warning but is sometimes preceded by feelings of dizziness or "swimming" in the head. The person's eyes are usually open but the person claims an inability to see. The person usually hears and understands what is occurring around him or her but feels powerless to move. This may correspond to a diagnosis of conversion disorder or a dissociative disorder.

ghost sickness A preoccupation with death and the deceased (sometimes associated with witchcraft) frequently observed among members of many American Indian tribes. Various symptoms can be attributed to ghost sickness, including bad dreams, weakness, feelings of danger, loss of appetite, fainting, dizziness, fear, anxiety, hallucinations, loss of consciousness, confusion, feelings of futility, and a sense of suffocation.

hwa-byung (also known as **wool-hwa-byung**) A Korean folk syndrome literally translated into English as "anger syndrome" and attributed to the suppression of anger. The symptoms include insomnia, fatigue, panic, fear of impending death, dysphoric affect, indigestion, anorexia, dyspnea, palpitations, generalized aches and pains, and a feeling of a mass in the epigastrium.

koro A term, probably of Malaysian origin, that refers to an episode of sudden and intense anxiety that the penis (or, in women, the vulva and nipples) will recede into the body and possibly cause death. The syndrome is reported in south and east Asia, where it is known by a variety of local terms, such as *shuk yang, shook yong,* and *suo yang* (Chinese); *jinjinia bemar* (Assam); or *rok-joo* (Thailand). It is occasionally found in the West. Koro at times occurs in localized epidemic form in east Asian areas. The diagnosis is included in the second edition of *Chinese Classification of Mental Disorders* (CCMD-2).

latah Hypersensitivity to sudden fright, often with echopraxia, echolalia, command obedience, and dissociative or trancelike behavior. The term *latah* is of Malaysian or Indonesian origin, but the syndrome has been found in many parts of the world. Other terms for the condition are *amurakh, irkunii, ikota, olan, myriachit,* and *menkeiti* (Siberian groups); *bah tschi, bah-tsi, baah-ji* (Thailand); *imu* (Ainu, Sakhalin, Japan); and *mali-mali* and *silok* (Philippines). In Malaysia it is more frequent in middle-aged women.

locura A term used by Latinos in the United States and Latin America to refer to a severe form of chronic psychosis. The condition is attributed to an inherited vulnerability, to the effect of multiple life difficulties, or to a combination of both factors. Symptoms exhibited by persons with locura include incoherence, agitation, auditory and visual hallucinations, inability to follow rules of social interaction, unpredictability, and possible violence.

mal de ojo A concept widely found in Mediterranean cultures and elsewhere in the world. *Mal de ojo* is a Spanish phrase translated into English as "evil eye." Children are especially at risk. Symptoms include fitful sleep, crying without apparent cause, diarrhea, vomiting, and fever in a child or infant. Sometimes adults (especially women) have the condition.

nervios A common idiom of distress among Latinos in the United States and Latin America. A number of other ethnic groups have related, though often somewhat distinctive, ideas of nerves (such as *nevra* among Greeks in North America). Nervios refers both to a general state of vulnerability to stressful life experiences and to a syndrome brought on by difficult life circumstances. The term *nervios* includes a wide range of symptoms of emotional distress, somatic disturbance, and inability to function. Common symptoms include headaches and brain aches, irritability, stomach disturbances, sleep difficulties, nervousness, easy tearfulness, inability to concentrate, trembling, tingling sensations, and *mareos* (dizziness with occasional vertigo-like exacerbations). Nervios tends to be an ongoing problem, although variable in the degree of disability that is manifest. Nervios is a very broad syndrome that spans the range from cases free of a mental disorder to presentations resembling adjustment, anxiety, depressive, dissociative, somatoform, or psychotic disorders. Differential diagnosis will depend on the constellation of symptoms experienced, the kind of social events that are associated with the onset and progress of nervios, and the level of disability experienced.

piblokto An abrupt dissociative episode accompanied by extreme excitement of up to 30 minutes' duration and frequently followed by convulsive seizures and coma lasting up to 12 hours. It is observed primarily in arctic and subarctic Eskimo communities, although regional variations in name exist. The person may be withdrawn or mildly irritable for a period of hours or days before the attack and will typically report complete amnesia for the attack. During the attack the person may tear off his or her clothing, break furniture, shout obscenities, eat feces, flee from protective shelters, or perform other irrational or dangerous acts.

qi-gong psychotic reaction A term describing an acute, time-limited episode characterized by dissociative, paranoid, or other psychotic or nonpsychotic symptoms that may occur after participation in the Chinese folk health-enhancing practice of qi-gong (exercise of vital energy). Especially vulnerable are persons who become overly involved in the practice. This diagnosis is included in the second edition of *Chinese Classification of Mental Disorders* (CCMD-2).

TABLE 15.3-2 (*continued*)

rootwork A set of cultural interpretations that ascribe illness to hexing, witchcraft, sorcery, or the evil influence of another person. Symptoms may include generalized anxiety and gastrointestinal complaints (e.g., nausea, vomiting, diarrhea), weakness, dizziness, the fear of being poisoned, and sometimes fear of being killed (voodoo death). Roots, spells, or hexes can be put or placed on other persons, causing a variety of emotional and psychological problems. The hexed person may even fear death until the root has been taken off (eliminated), usually through the work of a root doctor (a healer in this tradition), who can also be called on to bewitch an enemy. Rootwork is found in the southern United States among both African American and European American populations and in Caribbean societies. It is also known as *mal puesto* or *brujeria* in Latino societies.

sangue dormido ("sleeping blood") A syndrome found among Portuguese Cape Verde Islanders (and immigrants from there to the United States). It includes pain, numbness, tremor, paralysis, convulsions, stroke, blindness, heart attack, infection, and miscarriage.

shenjing shuairuo ("neurasthenia") In China a condition characterized by physical and mental fatigue, dizziness, headaches, other pains, concentration difficulties, sleep disturbance, and memory loss. Other symptoms include gastrointestinal problems, sexual dysfunction, irritability, excitability, and various signs suggesting disturbance of the autonomic nervous system. In many cases the symptoms would meet the criteria for a DSM-IV mood or anxiety disorder. The diagnosis is included in the second edition of *Chinese Classification of Mental Disorders* (CCMD-2).

shen-k'uei (Taiwan); **shenkui** (China) A Chinese folk label describing marked anxiety or panic symptoms with accompanying somatic complaints for which no physical cause can be demonstrated. Symptoms include dizziness, backache, fatigability, general weakness, insomnia, frequent dreams, and complaints of sexual dysfunction, such as premature ejaculation and impotence. Symptoms are attributed to excessive semen loss from frequent intercourse, masturbation, nocturnal emission, or passing of white turbid urine believed to contain semen. Excessive semen loss is feared because of the belief that it represents the loss of one's vital essence and can thereby be life threatening.

shin-byung A Korean folk label for a syndrome in which initial phases are characterized by anxiety and somatic complaints (general weakness, dizziness, fear, anorexia, insomnia, gastrointestinal problems), with subsequent dissociation and possession by ancestral spirits.

spell A trance state in which persons "communicate" with deceased relatives or with spirits. At times the state is associated with brief periods of personality change. The culture-specific syndrome is seen among African Americans and European Americans from the southern United States. Spells are not considered to be medical events in the folk tradition, but may be misconstrued as psychotic episodes in clinical settings.

susto ("fright," or "soul loss") A folk illness prevalent among some Latinos in the United States and among people in Mexico, Central America, and South America. Susto is also referred to as *espanto, pasmo, tripa ida, perdida del alma,* or *chibih.* Susto is an illness attributed to a frightening event that causes the soul to leave the body and results in unhappiness and sickness. Persons with susto also experience significant strains in key social roles. Symptoms may appear any time from days to years after the fright is experienced. It is believed that in extreme cases, susto may result in death. Typical symptoms include appetite disturbances, inadequate or excessive sleep, troubled sleep or dreams, feelings of sadness, lack of motivation to do anything, and feelings of low self-worth or dirtiness. Somatic symptoms accompanying susto include muscle aches and pains, headache, stomachache, and diarrhea. Ritual healings are focused on calling the soul back to the body and cleansing the person to restore bodily and spiritual balance. Different experiences of susto may be related to major depressive disorder, posttraumatic stress disorder, and somatoform disorders. Similar etiological beliefs and symptom configurations are found in many parts of the world.

taijin kyofu sho A culturally distinctive phobia in Japan, in some ways resembling social phobia in DSM-IV. The syndrome refers to a person's intense fear that his or her body, its parts or its functions, displease, embarrass, or are offensive to other people in appearance, odor, facial expressions, or movements. The syndrome is included in the official Japanese diagnostic system for mental disorders.

zar A general term applied in Ethiopia, Somalia, Egypt, Sudan, Iran, and other North African and Middle Eastern societies to the experience of spirits possessing a person. Persons possessed by a spirit may experience dissociative episodes that may include shouting, laughing, hitting the head against a wall, singing, or weeping. They may show apathy and withdrawal, refusing to eat or carry out daily tasks, or may develop a long-term relationship with the possessing spirit. Such behavior is not considered pathological locally.

Because of those complications, it is often difficult to determine whether paranoid experiences among recent immigrants and sojourners are reactive in nature or indicate a more serious psychotic process.

PHYSIOLOGICAL FACTORS Physical conditions—such as cerebral neoplasms, particularly of the occipital or temporal areas—can induce hallucinations. Sensory deprivation, as occurs in blind and deaf persons, can also result in hallucinatory or delusional experiences. Lesions involving the temporal lobe and other cerebral regions, especially the right hemisphere and the parietal lobe, are often associated with delusions.

Psychoactive substances are common causes of psychotic syndromes. The most commonly involved substances are alcohol, indole hallucinogens—for example, lysergic acid diethylamide (LSD), amphetamine, cocaine, mescaline, phencyclidine (PCP), and ketamine. Many other substances, including steroids and thyroxine, can be associated with substance-induced hallucinations.

DIAGNOSIS AND CLINICAL FEATURES

ICD-10

Acute polymorphic psychotic disorder without symptoms of schizophrenia Acute polymorphic psychotic disorder without symptoms of schizophrenia is characterized by obvious but variable and rapidly changing hallucinations, delusions, and perceptual disturbances, often accompanied by emotional turmoil (happiness and ecstasy or anxiety and irritability). The criteria for manic episode, depressive episode, or schizophrenia are not met. The disorder tends to have an abrupt onset (less than 48 hours) and then a rapid resolution of symptoms. If those persist for more than three months, the diagnosis should be changed (for example, to persistent delusional disorder or some other nonorganic psychotic disorder). It accommodates the concepts of *bouffée délirante* and cycloid psychosis, both either unspecified or without symptoms of schizophrenia.

Acute polymorphic psychotic disorder with symptoms of schizophrenia Acute polymorphic psychotic disorder with symptoms of schizophrenia is as polymorphic as the preceding disorder, but is additionally characterized by the consistent presence of typical schizophrenic symptoms. If the schizophrenic symptoms last more than one month, the diagnosis should be changed to schizophrenia. The disorder accommodates the concepts of *bouffée délirante* and cycloid psychosis, both with symptoms of schizophrenia.

Acute schizophrenialike psychotic disorder Acute schizophrenia-like psychotic disorder is characterized by the consistent and stable presence of typical schizophrenic symptoms, without the polymorphic character of the foregoing dis-

orders. If the schizophrenic symptoms last more than one month, the diagnosis should be changed to schizophrenia.

Other acute predominantly delusional psychotic disorders The other disorders are characterized by relatively stable delusions or hallucinations, without fulfilling the criteria for either schizophrenia or the acute polymorphic psychotic disorders. If the delusions persist for more than three months, the diagnosis should be changed to persistent delusional disorder, and if only the hallucinations persist, to other nonorganic psychotic disorder. The disorder accommodates the concepts of psychogenic paranoid psychosis and paranoid reaction.

Other acute and transient psychotic disorders The category includes other acute psychotic disorders not classifiable under the preceding categories, provided there is no evidence of an organic cause. Examples include acute psychoses with definite but fleeting delusions or hallucinations, and states of undifferentiated excitement.

Acute and transient psychotic disorder, unspecified The residual category accommodates such concepts as brief reactive psychosis not otherwise specified.

DSM-IV

Psychotic disorder due to a general medical condition The DSM-IV diagnosis of psychotic disorder due to a general medical condition (Table 15.3-3) combines into one diagnosis the two similar diagnostic categories in the revised third edition of DSM (DSM-III-R), organic delusional disorder and organic hallucinosis. The phenomena of the psychotic disorder are defined in DSM-IV by further specifying the predominant symptoms. When the diagnosis is used, the medical condition, along with the predominant symptom pattern, should be included in the diagnosis—for example, psychotic disorder due to a brain tumor, with delusions. The DSM-IV criteria further specify that the disorder does not occur exclusively while the patient is delirious or demented and that the symptoms are not better accounted for by another mental disorder.

Substance-induced psychotic disorder DSM-IV has combined the various DSM-III-R diagnostic categories that relate to psychoactive substance-induced psychotic disorders into a single diagnostic category, substance-induced psychotic disorder (Table 15.3-4). The diagnosis is reserved for persons who have substance-induced psychotic symptoms in the absence of reality testing. Persons who have substance-induced psychotic symptoms (for example, hallucinations) but who have retained reality testing should be classified as having a substance-related disorder—for example, phencyclidine intoxication with perceptual disturbances. The intent of including the diagnosis of substance-induced psychotic disorder with the other psychotic disorder diagnoses is to prompt the clinician to consider the possibility that a substance is causally involved in the production of the psychotic symptoms. The full diagnosis of substance-induced psychotic disorder should include the type of substance involved, the stage of substance use when the disorder began (for example, during intoxication or withdrawal), and the clinical phenomena (for example, hallucinations or delusions).

Psychotic disorder not otherwise specified The psychotic disorder not otherwise specified (NOS) category is used for patients who have psychotic symptoms (for example, delusions, hallucinations, and disorganized speech and behavior)

TABLE 15.3-3
Diagnostic Criteria for Psychotic Disorder Due to a General Medical Condition

A. Prominent hallucinations or delusions.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
C. The disturbance is not better accounted for by another mental disorder.
D. The disturbance does not occur exclusively during the course of a delirium.

Code based on predominant symptom:
With delusions: if delusions are the predominant symptom
With hallucinations: if hallucinations are the predominant symptom

Coding note: Include the name of the general medical condition on Axis I, e.g., psychotic disorder due to malignant lung neoplasm, with delusions; also code the general medical condition on Axis III.

Coding note: If delusions are part of a preexisting dementia, indicate the delusions by coding the appropriate subtype of the dementia if one is available, e.g., dementia of the Alzheimer's type, with late onset, with delusions.

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 15.3-4
Diagnostic Criteria for Substance-Induced Psychotic Disorder

A. Prominent hallucinations or delusions. **Note:** Do not include hallucinations if the person has insight that they are substance-induced.
B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
   (1) the symptoms in criteria A developed during, or within a month of, substance intoxication or withdrawal
   (2) medication use is etiologically related to the disturbance
C. The disturbance is not better accounted for by a psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a psychotic disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced psychotic disorder (e.g., a history of recurrent non-substance-related episodes).
D. The disturbance does not occur exclusively during the course of a delirium.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

Code: [Specific substance]-induced psychotic disorder (Alcohol, with delusions; alcohol, with hallucinations; amphetamine [or amphetaminelike substance], with delusions; amphetamine [or amphetaminelike substance], with hallucinations; cannabis, with delusions; cannabis, with hallucinations; cocaine, with delusions; cocaine, with hallucinations; hallucinogen, with delusions; hallucinogen, with hallucinations; inhalant, with delusions; inhalant, with hallucinations; opioid, with delusions; opioid, with hallucinations; phencyclidine [or phencyclidinelike substance], with delusions; phencyclidine [or phencyclidinelike substance], with hallucinations; sedative, hypnotic or anxiolytic, with delusions; sedative, hypnotic or anxiolytic, with hallucinations; other [or unknown] substance, with delusions; other [or unknown] substance, with hallucinations)

Specify if:
With onset during intoxication: if criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome
With onset during withdrawal: if criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, a withdrawal syndrome

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

TABLE 15.3-5
Diagnostic Criteria for Psychotic Disorder Not Otherwise Specified

This category includes psychotic symptomatology (i.e., delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior) about which there is inadequate information to make a specific diagnosis or about which there is contradictory information, or disorders with psychotic symptoms that do not meet the criteria for any specific psychotic disorder.
Examples include:
1. Postpartum psychosis that does not meet criteria for mood disorder with psychotic features, brief psychotic disorder, psychotic disorder due to a general medical condition, or substance-induced psychotic disorder
2. Psychotic symptoms that have lasted for less than one month but that have not yet remitted, so that the criteria for brief psychotic disorder are not met
3. Persistent auditory hallucinations in the absence of any other features
4. Persistent nonbizarre delusions with periods of overlapping mood episodes that have been present for a substantial portion of the delusional disturbance
5. Situations in which the clinician has concluded that a psychotic disorder is present, but is unable to determine whether it is primary, due to a general medical condition, or substance induced

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

but who do not meet the diagnostic criteria for other specifically defined psychotic disorders. In some cases the diagnosis of psychotic disorder not otherwise specified may be used when not enough information is available to make a specific diagnosis. DSM-IV has listed some examples of the diagnosis to help guide clinicians (Table 15.3-5).

CULTURE INFLUENCES ON THE MANIFESTATION OF PSYCHOSES In addition to those enumerated above, there are many factors that make the cross-cultural assessment of psychotic patients particularly challenging. Cross-ethnic differences in emotional expressiveness have been well documented in the literature and may hinder the assessment of affect and behavior in such a way that a culturally appropriate range of expression may be mistaken as evidence of flat affect or emotional withdrawal. Relative to the clinician's standard for the normal range of affect, the patient's reports may be either overestimated or underestimated in their significance.

The clinician's interpretation of the patient's complaints tends to be framed by the official nosological system. That raises the question of the validity of the diagnostic system used. Although greater efforts have been made to base the construction of the new standard manuals on sounder epidemiological data and to reflect greater attention to cultural factors, major limitations remain in both the balance of conceptualization and the adequacy of field trials.

Ms. A., a 27-year-old, single woman, was brought to the emergency room of a community hospital in California because of acute onset of agitation, shouting, refusal of food and drink, and fear of impending death. Brought up in Ethiopia as a Coptic Christian, she had lived a sheltered life until approximately five years before evaluation, when the family (parents and 11 siblings) became victims of civil war. Along with some relatives, she escaped to Kenya and eventually resettled in the Los Angeles area, joining a brother who had migrated there many years earlier. They had apparently lost contact with the rest of the family.

Her life in the United States in the past three years had not been easy. Her attendance at classes in English as a Second Language was erratic, with limited progress. She was, in general, quite isolated, not only from mainstream society, but also from the local Ethiopian community. Several months earlier, she had started working as a housekeeper, but quit abruptly just prior to the current episode, apparently because of persecutory fears. She had no prior history of contact with psychiatric services. However, in Kenya she was once taken to see a "medicine man," who told her that there were people around her who were trying to "poison" her. Since arriving in the United States, she had mentioned several times that someone might try to poison and kill her, without describing those suspicions in detail.

In the hospital she at first appeared extremely agitated and delusional, and she reported that her mother, who she thought had died in Ethiopia, had talked to her and warned her of impending dangers. She also admitted to Schneiderian-like thought insertion and to hearing voices commenting on her behavior. However, language difficulties made questionable the validity of those symptoms. Two days after treatment with small doses of antipsychotics most of the symptoms had disappeared. She became calm and cooperative, with some restriction in affect. She was promptly discharged and followed up at a local outpatient clinic where the medication was discontinued because of her complaints of side effects. Three months later she dropped out of the clinic. At her last visit she was asymptomatic and was working again as a housekeeper.

Diagnostic assessment presented a challenge to the clinicians involved. Although a schizophrenic process was suspected, there were many quandaries. Paranoid symptoms were partially explainable by the woman's life experiences and her culturally sanctioned beliefs about sorcery, reinforced by the medicine man she had seen in Kenya. Hearing her deceased mother's voice could be culturally congruent. Although her social isolation and low level of functioning before the episode could be construed as prodromal signs of schizophrenia, they could equally be the result of her difficulty in adjusting to an alien, technologically complex culture. Last, the clinical course was also not congruent with a diagnosis of schizophrenia. With an abrupt onset, rapid response to treatment, and almost complete recovery, the case more closely resembled the archetype of *bouffée délirante* often observed in West Africa and Haiti. It could perhaps be accommodated within ICD-10 as an acute polymorphic psychotic disorder with symptoms of schizophrenia.

CULTURE-BOUND SYNDROMES Perhaps the most dramatic example of the difficulties in applying Western-based nosological concepts and criteria cross-culturally can be found in the ongoing controversy surrounding the culture-bound syndromes.

As pointed out recently by the United States National Institute of Mental Health Culture and Diagnosis Group, the term "culture-bound syndrome" denotes recurrent, locality-specific patterns of aberrant behavior and troubling experiences that appear to fall outside conventional Western psychiatric categories. Those include categories in folk nosological systems (often organized in relation to perceived cause and symptom clusters) as well as idioms of distress or culturally salient expressions for securing social support and communicating symptoms. Terms formerly used to refer to such phenomena include "cultural and ethnic psychoses and neuroses" and "atypical and exotic psychotic syndromes." Because the experience and expression of psychiatric illness are always influenced by cultural factors, those terms are evidently problematic.

Amok Although "running amok" has become a common English expression, most people are not aware of its origin as a Malayan term referring to a violent or furious fit with homicidal intent. The syndrome of amok may be defined by four major characteristics: prodromal brooding, homicidal outburst, persistence in reckless killing without apparent motive, and a claim of amnesia. The attack, which often results in multiple casualties, is usually terminated only when the afflicted person becomes totally exhausted or is captured or killed.

Amok and its related terms, *mengamok* (the act of running amok), *pengamok* (the amoker), *gila mengamok* (amok psychosis), and *mata gelap* (darkened eye), are familiar concepts to the Malays. The amokers are believed almost always to be young men whose self-esteem has been severely injured. Although they traditionally are not held responsible for their acts, they nevertheless are either confined or ostracized for fear of recurrences. It has been suggested that amok constitutes a

behavioral alternative in reaction to the heavy emphasis in Malay culture on hierarchy, appropriateness, and nonaggression. The belief that someone may actually become an amoker (if pushed to the extreme) may also serve to curb the excessive use of power by those in positions of authority.

Attacks of sudden mass assault with amoklike behavior and consequences are not limited to the Malay cultural sphere, having been reported throughout Southeast Asia, as well as in North America and the Caribbean area. Similar syndromes are *mal de pelea* in Puerto Rico and *iich' aa* among the Navajos. The available literature suggests that those cases share with Malay amokers some important demographic (age and gender), psychosocial (perceived humiliation as precipitant), and perhaps psychodynamic (difficulties with independence and aggression) characteristics.

Koro Koro is usually manifest as an episode of sudden and desperate fear that the penis (or less commonly, the vulva and breasts in women) is shrinking and may recede into the abdomen, possibly causing death. During the attack patients typically experience intense fear and panic associated with cold sweat, paresthesias, palpitations, weakness, skin pallor, visual blurring, and faintness. In their attempt to prevent the complete retraction of the penis, and hence death, they hold on to the penis either manually or with the aid of strings or clamps. Family members, relatives, and friends often take turns holding the penis to prevent its shrinking.

Koro is a Malay term of uncertain origin. First reported by Dutch physicians working in western Sulawesi (formerly known as Celebes, an island of Indonesia), in recent years the condition has been observed predominantly among Chinese residing in Southeast Asia and southern China, where it has been known as *suoyang* (*suo:* retract; *yang:* penis). More recently, korolike conditions have also been observed in Mindanao (an island in the southern part of the Philippines, neighboring Indonesia), northern Thailand, and northeast India. Among the Chinese, the syndrome is deeply imbedded in traditional medical theories, including the yin-yang humoral balance, the importance of the conservation of vital energy, the value of semen as the purest (and thus most precious) form of vital energy, and the belief that the complete retraction of the penis results in death. Practically all Chinese koro (suo yang) cases report preexisting worries about what the sufferers consider sexual excesses, such as nocturnal emission, masturbation, or sexual overindulgence. Many cases are precipitated by unhealthy coitus (for example, with prostitutes), sudden exposure of the penis to cold water or cold air, or hearing about people dying from koro. Reflecting its widely held importance, the condition is included in the second edition of the *Chinese Classification of Mental Disorders* (CCMD-2).

In addition to individual cases, koro has also been observed in epidemic forms, typically in communities experiencing heightened social or political tension. For example, in 1967, at the height of the Malay-Chinese conflict in Malaysia, more than 400 Chinese developed koro within five days after hearing the rumor that the pork that they had eaten had been deliberately infected with swine fever. More recent epidemics in Thailand and India were similarly precipitated by political rumors (for example, that Vietnamese soldiers had poisoned the water to make Thai men impotent).

Sporadic cases involving intense fear of penile retraction have been reported in Western countries and in Africa. However, those cases lack the cultural elaboration of true koro cases. Sufferers do not associate their experiences with the belief of impending death, and episodes are more likely to appear in the context of major psychiatric conditions, such as organic brain syndromes, schizophrenia, drug-induced psychosis, and mood disorders.

Latah *Latah* is a Malay term for the hypersensitivity to sudden fright or startle. In those afflicted a sudden stimulus typically provokes the suspension of all normal activities and triggers involuntary motor and verbal reactions that are stereotypical and socially inappropriate (for example, coprolalia). In more severe cases the hypersensitivity to startle is also accompanied by mimetic or echo symptoms, including echolalia, echopraxia, and automatic obedience.

Latah affects both men and women although most are middle-aged women of relatively low or marginal social status. The syndrome is often precipitated by major stressful life events. Social conditioning may also contribute to the onset of the condition, because in a Malayan setting those with a tendency to startle are repeatedly poked or teased. Most latah sufferers are embarrassed and ashamed of their problems, and many tend to shy away from social interactions to avoid the teasing and the provocation of latah behavior. Others appear to enjoy the attention they receive with their latah performances. For them latah may provide an important social role that satisfies their intrapsychic needs.

Conditions similar to latah have been reported in other cultures, including *imu* among the Ainu in northern Japan; *myriachit, ikota,* and *amurakh* in Siberia; *bah tschi* in Thailand, and *mali-mali* in the Philippines.

Taijin kyofu sho The Japanese term means "fear of facing or interacting with other people," not necessarily fear of people. Patients suffering from the condition experience a profound fear—often reaching seemingly psychotic proportions—of hurting the feelings of others, with certain shortcomings within themselves. Those shortcomings include a real or imagined propensity to blush, to gaze inappropriately at others, to emit (most often imaginary) body odors, or to shake or to tense up involuntarily in front of others. Most taijin kyofu sho (TKS) patients are adolescent boys and young adult men. Despite the intensity of their symptoms and the near-delusional quality of their obsessions, they are typically engaging and eager to cooperate during clinical interviews, and they show a strong desire to be with other people rather than to avoid them. Clinicians have great difficulty placing TKS patients in any standard diagnostic category because their symptoms are simultaneously suggestive of obsessive-compulsive disorder, somatoform disorder, and even psychotic disorder. Although the core symptom of the condition, the fear of social situations, is similar to what is seen in standard social phobia, the conditions are distinctively different. Differences include not only the prevalence and severity of symptoms, the degree of disability associated with the condition, and demographic characteristics (predominantly younger men), but the subjective meaning of the symptoms. TKS patients' primary concern not to embarrass or inconvenience others reflects the group orientation of Japanese culture, and it is harder to understand within the Western individualistic context, where most patients with social phobia are primarily worried about being embarrassed or ridiculed. The syndrome is included in the *Japanese Clinical Modification* of ICD-10.

Piblokto Occurring among Eskimos and sometimes referred to as Arctic hysteria, *piblokto* is characterized by attacks lasting from one to two hours, during which patients (usually women) begin to scream and to tear off and destroy their clothing. While imitating the cry of some animal or bird, the patients may throw

themselves on the snow or run wildly about on the ice, although the temperature may be well below zero. After the attack the person appears to be normal and usually has no memory of the episode. The Eskimos are reluctant to touch afflicted persons during the attacks because they believe that the attacks involve evil spirits. Piblokto appears to be a hysterical state of a dissociative disorder. It has become much less frequent than it used to be among Eskimos.

Qi-gong psychotic reaction Qi-gong (exercise of vital energy) is an age-old Chinese self-healing practice with features of meditation and kung-fu that in recent years has gained a great deal of popularity in practically all Chinese communities, including mainland China, Hong Kong, Taiwan, and those in North America. In mainland China an estimated 10 percent of the more than one billion citizens practice qi-gong on a regular basis. Based on the traditional Chinese belief in the importance of *qi* (or *chi*, which means vital energy) circulation, both within the body and between the body and its natural environment, such exercises are supposed to improve one's physical, mental, and spiritual health by reducing the stagnation of the qi circulation. While performing the exercises, practitioners often experience a special sensation of qi's following the meridian routes through the body. Since the belief also involves the exchange of qi between the exerciser and the environs and, through the environs, with other people, some qi-gong practitioners also believe that it is not only a self-healing practice but can also be used to heal others.

Regular practice of qi-gong is believed to result in a sense of well-being and to be effective in reducing stress and various psychological and psychophysiological symptoms. However, qi-gong is clearly not an innocuous practice because if done inappropriately (according to its enthusiasts), it can induce adverse side effects, ranging from transient, minor symptoms (for example, an increase in anxiety) to persistent psychotic symptoms, including hallucinations and delusions. With the growing popularity of the practice in China, the prevalence of the qi-gong psychotic reaction has apparently greatly increased, to the extent that it has become necessary for Chinese psychiatrists to include it in CCMD-2.

Voodoo, rootwork, and related states Behavioral disturbances associated with possession phenomena are observed in many cultural settings and are given different names (for example, *zar, mal puesto, shin-byung*). Voodoo hexing is the most widely known and discussed, not only by anthropologists and psychiatrists, but also by popular writers and others. Originating in West Africa, voodoo cult practices can be found in many parts of Africa, the Caribbean region, and Latin America, and they are particularly widespread in Haiti. Victims of voodoo curses are believed to succumb to voodoo death, and then to be brought to life again by voodoo doctors or those who possess the voodoo power. The living dead are believed totally to lack self-awareness and self-initiation and to be controlled completely by those with the voodoo power. The phenomenon of voodoo death has been the subject of intense research and speculation, and various explanatory theories have been postulated, including poisoning, dehydration, stress-induced cardiac arrhythmia, the overstimulation of the sympathetic and parasympathetic nervous systems, and the giving up–given up complex.

Voodoo death is a relatively rare event even in voodoo-endemic areas, such as Haiti. However, the belief in voodoo power is widespread and deeply rooted among persons of African descent in the Caribbean area. The same appears to be true in the case of rootwork, a similar belief prevalent in certain parts of the South in the United States.

Wihtigo *Wihtigo*, or windigo psychosis, is a psychiatric disorder confined to the Cree, Ojibwa, and Salteaux Indians of North America. Affected persons believe that they may be transformed into a wihtigo, a giant monster that eats human flesh, and during times of starvation, may feel and express a craving for human flesh. Because of the patient's belief in witchcraft and in the possibility of such a transformation, symptoms affecting the alimentary tract, such as loss of appetite and nausea from trivial causes, may cause the patient to become greatly excited for fear of being transformed into a wihtigo.

PATHOLOGY AND LABORATORY EXAMINATION

A large number of general medical problems may cause or exacerbate patients' psychotic conditions, often involving confusing and puzzling presentations. They include such conditions as infections (including human immunodeficiency virus [HIV] infection), head trauma, endocrine disorders (Cushing's and Addison's diseases and disorders of the thyroid and parathyroid glands), autoimmune diseases (systemic lupus erythematosus), vitamin deficiencies, seizure disorders, genetic diseases (Wilson's disease, acute intermittent porphyria), drug and toxin exposures, and the effects of psychoactive drugs. Those conditions are usually included in the differential diagnosis of any psychotic disorder, but they should be given more careful consideration when the patient's symptom profile is polymorphic or inchoate. For such patients laboratory tests should include not only the routine chemistry panels (electrolytes, glucose, complete blood counts, renal and liver functions) and urinalysis, but also thyroid function tests, syphilis tests, and determination of serum cortisol levels, vitamin B_{12} and foliate levels, and calcium and phosphate levels. In addition to a chest X-ray and an electrocardiogram (ECG), an electroencephalogram (EEG) should also be considered. An EEG with sleep deprivation and nasopharyngeal leads also has been recommended. Computerized EEG (brain mapping), magnetic resonance imaging (MRI), single photon emission computered tomography (SPECT), and neuropsychological testing may yield useful information.

Psychosocial assessment should include a careful review of the patient's life history, with special attention to the patient's personality traits and recent stresses. A detailed assessment of family history and dynamics should also be included. Contextual factors, such as psychosocial stressors and supports, should be carefully appraised, along with the ability of the person to perform basic roles (for example, occupationally, with family, and socially).

COURSE AND PROGNOSIS

In patients with an acute and transient psychotic disorder, complete recovery usually occurs within one to three months (depending on the specific disorder), often within a few weeks or days, and only a small proportion of patients develop persistently disabling states.

Limited data on the longitudinal course of patients with culture-bound syndromes have suggested that some of them eventually develop clinical features compatible with a diagnosis of schizophrenia, bipolar disorder, cognitive disorder, or other psychotic disorders. It is thus crucial to gather information from all possible sources. Since clinical pictures evolve over time,

thorough reevaluations should be conducted periodically to enable an accurate diagnosis and effective clinical care.

TREATMENT

Careful evaluation, clinical observation, and comprehensive information gathering are the cornerstones of treatment planning for any psychiatric or general medical disorder. Comprehensive and longitudinal assessments are of particular importance in the management of patients who are experiencing acute and transient psychotic disorders and culture-bound disorders.

A multiaxial assessment using such schemas as those in ICD-10 and DSM-IV can be very helpful in effective treatment planning. A complementary cultural formulation, such as the one recommended in DSM-IV, can substantially enhance diagnosis and clinical care. Such a formulation involves appraising the cultural identity of the patient, the cultural framework of illness and its context and implications, and intercultural elements in the clinician-patient relationship.

The treatment plan for any patient must be individualized, but that principle is particularly important when dealing with cases of acute and transient psychotic disorders and culture-bound psychotic disorders. Because of the intricate and heterogeneous nature of those conditions, there is no standard treatment strategy that can be applied to the majority of the cases.

Because a common denominator of all the disorders discussed in this section is the presence of psychosis, pharmacotherapy frequently involves the use of antipsychotic drugs. There is some evidence that the dosage of antipsychotics necessary for acute transient psychotic disorders is significantly lower than that required for other psychotic conditions, especially schizophrenia. It is thus prudent to use the lowest dose that can control the patient's symptoms. Since acute and transient psychotic disorders are often episodic, the intermittent use of antipsychotics, guided by the emergence of psychotic symptoms, is worth considering.

Depending on the clinical features of particular cases, many other psychiatric medicines have also been recommended. They include benzodiazepines for controlling agitation, lithium (Eskalith) for modulating mood swings, and antidepressants for ameliorating depressive symptoms, and are often used in conjunction with antipsychotics. Anticonvulsants, such as carbamazepine (Tegretol), have been reported to have been effective in treating a number of psychotic patients with atypical features.

Limited research has been conducted to date on the efficacy of various psychosocial interventions for managing acute and transient psychotic disorders and culture-bound disorders. It appears reasonable to consider findings from studies involving other psychotic conditions. Those include approaches based on expressed emotion concepts, psychoeducational and skill-competence training, and Thomas McGlashan's phase-specific theory on the need for stimulation in schizophrenic patients (the avoidance of excessive stimuli in the acute phase and the uses of structured activities and stimuli in later phases). It is important to consider involving the family in therapy and to establish a supportive and trusting therapeutic relationship.

The importance of cultural issues in the evaluation and treatment of atypical psychoses can hardly be exaggerated, especially when dealing with patients from non-Western and ethnic minority populations. Cultural information not only is crucial for accurate diagnosis, but also is indispensable in the formulation of treatment plans. Treatment approaches that do not take the patient's sociocultural background into account are likely to fail no matter how well intentioned the therapists may be. For example, in cultures in which family and group harmony and unity are valued over individual independence, the rigid application of Western-based psychotherapeutic techniques may exacerbate, rather than ameliorate, the patient's psychopathological condition. Consideration of the intercultural elements in the clinician-patient relationship is also fundamental for the establishment of rapport and the effective engagement of the patient and the family in the treatment process.

One promising avenue is collaboration with indigenous healers. Several researchers have reported on their success in the use of indigenous and traditional healers in the treatment of psychiatric patients, especially those whose psychotic conditions are substantially connected to culture-specific beliefs (for example, fear of voodoo death). Others have mentioned the potential pitfalls and problems in such collaboration. Decisions about involving indigenous healers should be individualized and thoughtfully planned, taking into consideration the setting, the sophistication and flexibility of the available healers, the type of psychopathology, and the patient's characteristics. The WHO has long advocated the implementation at the local level of a policy of close collaboration between the health system and traditional medicine, and, in particular, between individual health professionals and traditional practitioners.

SUGGESTED CROSS-REFERENCES

The influences of culture on the nature of and responses to psychiatric disorders are discussed in Section 4.2 on sociology and psychiatry. Section 4.3, on sociobiology and psychiatry, is also relevant. Section 11.2 concerns international perspectives on psychiatric diagnosis. Section 15.1 is devoted to other psychotic disorders, including brief psychotic disorder. Sociocultural aspects of geriatric psychiatry are the subject of Section 49.4b.

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15.4 POSTPARTUM PSYCHIATRIC SYNDROMES

BARBARA L. PARRY, M.D.

INTRODUCTION

Postpartum psychiatric illnesses are an underrecognized, undertreated, and underresearched area. One reason for the lack of attention to the disorders may be that postpartum psychiatric illnesses were not recognized as specific disorders before the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), reportedly because the disorders were not considered to have distinguishing features.

Postpartum psychiatric syndromes are listed as onset specifiers under mood disorders. The specifier with postpartum onset can also be applied to brief psychotic disorder. Unfortunately, going against the recommendation of the advisory members, the work group specified that the onset of the episode must be within four weeks postpartum. Although most psychotic episodes do have their onset within four weeks postpartum, many depressive episodes occurring postpartum have an insidious onset beginning three to four months postpartum.

DEFINITION

Postpartum psychiatric syndromes are mental illnesses that occur primarily as psychotic and nonpsychotic mood disorders. By the definition of the Marcé Society (an international society for the understanding, prevention, and treatment of mental illness related to childbearing), the illnesses have their onset within the first year after childbirth (in contrast to DSM-IV's cutoff point of four weeks). Most postpartum psychiatric syndromes, once organic factors are ruled out, are mood disorders. In DSM-IV, both psychotic and nonpsychotic major depressions and manías that occur postpartum are categorized as specifiers under the mood disorders section. In the revised third edition (DSM-III-R) postpartum psychiatric illness was not listed as a separate category but was listed under psychotic disorder not otherwise specified (atypical psychosis). Little attention was paid to postpartum psychiatric illness in the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10). Table 15.4-1 presents the DSM-IV criteria for postpartum onset specifier.

TABLE 15.4-1
Criteria for Postpartum Onset Specifier

Specify if:
With postpartum onset (can be applied to the current or most recent major depressive, manic, or mixed episode in major depressive disorder, bipolar I disorder, or bipolar II disorder; or to brief psychotic disorder)
Onset of episode within four weeks postpartum

Table from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994. Used with permission.

HISTORY

Psychiatric illnesses after childbearing have many unique qualities that distinguish them from other kinds of psychiatric illnesses. The phenomenon was noticed and documented by the French physician Louis Victor Marcé, whose 1858 treatise on peripartum mental illness dominated world thinking on those matters for a half-century. Marcé noted that postpartum illness displays a wide variety of symptoms, many of which appear in illnesses unrelated to childbearing. He noted, however, that the combinations of symptoms and signs, the syndromes of postpartum illness, are unique, as are the ways in which syndromes change, go into remission, only to be followed by an exacerbation or a different syndrome. He also noted that the manifestations of postpartum illness move in tandem with the then-known changes in female anatomy and physiology as women move from the pregnant to the nonpregnant state. Assessing those associations and the pervasive occurrence of confusion and delirium, Marcé was convinced that he was dealing with conditions with organic causes, conditions in which known physical and chemical factors interfere with cerebral functioning: fevers, toxins, and psychological states associated with known medical disorders. He saw the rapid changes in the generative system as a cause, but he was unable to find the mechanism that bridges the gap between the physical phenomena and the mind. He was so certain of the connection that he gave it a name, *sympathie morbide*. He wrote and died a quarter of a century before the outlines of the endocrine system began to become apparent. For the rest of the 19th century and a decade into the 20th century, many astute observers and investigators supplied many details regarding the unique and wide-ranging presentations of psychiatric illness after childbearing.

Some time after the turn of the century, a substantial part of the psychiatric profession shifted its interest from the care of severely and acutely ill patients to intensive psychotherapy for neurotic patients. Patients who required hospitalization were cared for in state and private facilities, where patients and staff members were at some distance from the mainstream of modern medicine. Classification became a dominant concern in the psychiatric facilities, and psychiatrists found little basis to follow the medical practice of naming and classifying patients according to cause. They fell back on a second choice, classification according to constellations of symptoms. Postpartum patients exhibited a wide and widely changing array of symptoms and syndromes. The complex and changing presentation of symptoms was regarded as threatening to the new classification system. The simple solution advocated by some leaders of psychiatry and affirmed officially in 1952 by the American Psychiatric Association in DSM-I was to strike out the term "postpartum" and all its synonyms from the nomenclature and to recommend that psychiatric disorders after childbearing be classified and named according to the symptoms or syndrome that was predominant at the time of the examination.

The consequences were a setback for patient care and for the advancement of knowledge in postpartum psychiatric illnesses. The vast majority of physicians, especially those in the fields of psychiatry and obstetrics, decided that responsible committees of knowledgeable physicians had come to the conclusion that postpartum illnesses did not exist and that childbirth had simply exposed latent functional illnesses, such as schizophrenia and bipolar disorder. That conclusion led to precepts that dominated most of medical thinking until the early 1980s: (1) It is folly to look for unique qualities in postpartum cases; at most, the cases are epiphenomena and only questionably relevant to etiology or treatment. (2) The developing armamentarium of psychotropic drugs is appropriate and sufficient for psychiatric illness after childbearing.

Research on postpartum psychiatric illness was almost nonexistent for most of the 20th century. Some suggestive leads from the late 19th century were disregarded. The vast majority of patients were treated with the same drugs and methods as their sisters with functional disorders. That situation continued until 1980, when Ian Brockington called a conference on postpartum mental illness in Manchester, England. Worldwide interest and concern were disclosed. Two hundred clinicians and investigators with interest in the matters formed the Marcé Society, an international scientific organization devoted to the psychiatric illnesses of new mothers. As a result, research throve, and ideas germinated.

Fifteen years is insufficient for a final doctrine of diagnosis, etiology, and treatment. Some competent investigators opine that there are many possible morbid mechanisms and that it is too early to select those most likely to be responsible for postpartum illness. They believe that many years of extensive experimentation must precede the decision to introduce specific medications directed toward presumed disease mechanisms.

Nevertheless, a historical perspective lends itself to the following observations: When clinical cases are studied and when data from related areas in clinical medicine, endocrinology, and clinical chemistry are reviewed, a remarkably simple pattern of pathophysiology emerges. The pattern has had a number of clinical trials and substandard experimental tests. There is support from many directions for the hypothesis that a causal relation exists between transitory hormonal deficits and two principal syndromes of postpartum mental illness, postpartum psychoses and postpartum major depression.

EPIDEMIOLOGY

POSTPARTUM PSYCHOSIS The frequency of postpartum psychosis in primiparous women (women who have given birth for the first time) is about 1 in 500. After a subsequent delivery, the risk for previously affected women is about 1 in 3.

POSTPARTUM NONPSYCHOTIC DEPRESSION The risk of nonpsychotic depression in primiparous women is 10 to 15 percent. The risk of recurrence is 50 percent in women without a prior history of a mood disorder and may approach 100 percent in those women with both a history of a mood disorder and a history of a previous postpartum major depressive disorder.

Maternity blues is not considered a disorder, since it generally occurs in 50 to 80 percent of women postpartum and because of the absence of major symptoms.

As several large-scale epidemiological studies have shown, the risk for major, hospitalizable mental illness during pregnancy is low—much lower than the expected rate in women not in the pregnant or postpartum state. However, the incidence of mental illness rises dramatically in the month after childbirth. That increased risk continues for six months to a year and in one study for up to two years postpartum. It is as though a protective factor against the onset of mental illness during pregnancy is released after childbirth.

ETIOLOGY

HORMONAL

Estradiol Since there is a marked elevation in estradiol during pregnancy, followed by an abrupt decline after parturition, a reasonable place to begin examining hormonal hypotheses of postpartum disorders is with this endocrine system. However, studies do not consistently show correlations between estradiol concentrations and postpartum blues, depression, or psychoses.

Progesterone One investigator claimed progesterone withdrawal as a cause of postpartum dysphoria on the basis of reports of the efficacy of progesterone treatment for the disorder and for premenstrual syndrome. However, that claim has not been substantiated by controlled clinical trials. Further substantive evidence for a progesterone deficiency as a basis for treating postpartum psychiatric syndromes is lacking. However, there are anecdotal reports of the efficacy of progesterone as a prophylactic treatment, although recent studies and progesterone's potential depressogenic side effects make it much less a viable prophylactic treatment than is lithium (Eskalith, Lithobid). Perhaps the therapeutic success achieved in those cases can be attributed to a change in progesterone-receptor sensitivity. The question needs rigorous clinical and biochemical evaluation.

Androgens In women both the ovaries and the adrenal cortex secrete the androgens testosterone and androstenedione. During pregnancy and lactation the cyclic variation of the ovarian secretion of those androgens is absent. Some studies report changes in levels of androgens associated with mood changes during the menstrual cycle and menopause. However, androgen therapy, given its masculinizing and depressive side effects, is warranted in postpartum depressive illness only for severe disorders and in those women who choose to refrain from breast feeding.

Cortisol Some of the hypotheses proposed to account for postpartum psychiatric disorders and possibly for other less severe syndromes include the following: The loss of the placenta at delivery is followed

by a precipitous fall in both serum estrogen and progesterone. Those changes are not directly responsible for extensive psychological symptoms, but they initiate processes that lead eventually to symptoms. The circulation, the mass, and the secretory activity of the pituitary gland are decreased markedly during the days immediately after delivery. Serum cortisol is elevated during the last trimester. The sluggish postpartum pituitary decreases its adrenocorticotropic hormone (ACTH) stimulation of the adrenal cortex, and that diminution acts to decrease the serum cortisol, with the free and physiologically active cortisol decreasing more rapidly than the cortisol bound to transcortin. The symptoms of the early, florid postpartum psychosis may be a response to a deficit below the threshold of cortical neuron tolerance. Extreme anxiety symptoms, often prominent in the early cases, is the result of stimulation of the autonomic centers in the hypothalamus by the extensive and repeated discharge of adjacent neurons that are sensors of low serum cortisol. The insomnia that is characteristic of the disorder follows the stimulation of the sleep centers adjacent to the cortisol sensors. The rapid but usually temporary remissions may be attributable to irregular discharges of ACTH that temporarily remedy the cortisol deficit.

Another chain of evidence indicates that temporary cortisol deficit plays a role in many cases of postpartum psychiatric illness. In 1858 Marcé noted that postpartum patients who failed to recover tended to have weakness, anemia, and peripheral edema. Other observers noted headache, sleep disturbances, decrease in blood pressure, hair and skin changes, amenorrhea, and marked weight changes, either gains or losses. Those physical signs are similar to the signs seen in chronic disorders of the pituitary and adjacent brain areas. In the mid-1950s an investigator noted a similarity between patients with early postpartum illness and patients who became psychotic after withdrawal from cortisone treatment. The investigator administered 10 to 15 mg of prednisolone daily for two to three weeks and reported successful treatment of 16 patients, as compared with a fairly comparable group of 16 control patients. In 1984 the investigator reported on 10 additional cases of early postpartum illness treated successfully with prednisolone.

SHEEHAN'S SYNDROME In 1967 the endocrine pathologist Howard Sheehan began reporting on postpartum necrosis of the anterior pituitary, a condition in which blood loss at delivery is followed by circulatory collapse of the pituitary. That collapse produces a wide array of multiglandular disorders as pituitary tropic hormones are lost. Worldwide research in the field was summarized in a 1982 monograph. Among the sequelae described are a wide variety of psychiatric syndromes, including agitation, delirium, hallucinations, delusions, and depression. The similarities to the range and the quality of postpartum illness are notable. The symptoms and the syndromes tend to group themselves into two major patterns, an early agitated condition and a dull depressive condition. The physical stigmata of postpartum necrosis of the pituitary, Sheehan's syndrome, are like those described as characteristic of cases of postpartum psychiatric illness that become chronic.

The foregoing findings and observations lead directly to the hypothesis that postpartum psychiatric illness may be related to Sheehan's syndrome, with the postpartum psychiatric illness caused by a temporary deficit in pituitary-controlled hormones from a sluggish postpartum pituitary and Sheehan's syndrome following extensive destruction of pituitary secretory cells. After decades of experimentation, it was determined that fairly effective treatment of Sheehan's syndrome was a daily dose of 35 mg of cortisone acetate and 0.3 mg of thyroxine. With that medication the psychiatric symptoms of Sheehan's syndrome were said to disappear within a few days. Those are virtually the same hormones as those reported to be effective for the late depression, the desiccated thyroid, and the early agitated state. The combination of thyroxine and a steroid has never been reported with psychiatric patients. For definitely established Sheehan's syndrome, neither thyroid alone nor cortisone alone yields satisfactory results.

The concept of Sheehan's syndrome and postpartum psychiatric illness now can be extended. They could be opposite poles of a continuum, with Sheehan's syndrome following extensive infarction and cellular destruction of the pituitary and with the psychiatric disorders reflecting a sluggish postpartum pituitary with temporary deficits in the production of hormones from glands responsive to deficits in pituitary tropic hormones. Both in Sheehan's syndrome and in the psychiatric disorders, the most important hormones in deficit appear to be cortisol and thyroxine.

OTHER PITUITARY DEFICITS If the psychiatric disorders and Sheehan's syndrome are on a continuum, intermediate cases can be expected. When they are looked for, they seem to appear. Two investigators described a case of postpartum depression that was later found to have a half-empty sella turcica. In retrospect, some of the cases of chronic psychiatric illness described probably had pituitary damage. Marcé cited extensive loss of blood at delivery as one of the causes of postpartum *folie*.

Excessive bleeding is not necessary for a marked diminution of pituitary function to occur. Exquisite drawings of pituitary changes during pregnancy and the normal puerperium were published early in this century. Between delivery and a few days postpartum, the pituitary exhibits a markedly diminished size and blood supply and a marked decrease in the number of secretory cells. Secretory granules all but disappear.

The sequence of psychiatric symptoms relates to the possible influence of hormonal deficit. After three days but during the first fortnight after delivery, florid psychotic symptoms tend to make their appearance. After three weeks, depressive syndromes develop. Some cases have both types of psychiatric disorder, with an early florid psychosis moving gradually into a depression.

The hormonal sequence in the puerperium is this: Both serum cortisol and thyroxine are high at delivery and then begin to fall. Both hormones are still well above the prepregnancy level at the third day. Nevertheless, psychiatric symptoms of the early agitated syndrome or psychosis may emerge rapidly at or soon after the third day. However, physiologically significant deficits may occur in free cortisol. After delivery, free cortisol tends to fall off more rapidly than does bound cortisol. Cerebral impairment from free cortisol deficit could be the critical factor in the production of the mercurial early postpartum psychosis.

Recent studies do not consistently show differences in measurable cortisol between symptomatic and asymptomatic patients, although most of the symptomatic patients sampled were suffering from maternity blues, not postpartum psychoses. The studies, however, are limited by the lack of circadian sampling, which may indicate changes in the diurnal profile of cortisol secretion. Furthermore, patients with maternity blues, although more accessible to study, are not suffering from a major mood disorder, in which altered neuroendocrine profiles may be readily apparent.

Since baseline studies often do not indicate abnormalities that reveal themselves only when the system in question is challenged by experimental perturbations, it is worth examining the results of the dexamethasone-suppression test (DST), which challenges the glucocorticoid system, in patients with postpartum mood disturbances. However, since normal control women show a high incidence of altered DST responses in the immediate postpartum period, the DST cannot be considered a valid descriminator of postpartum depression, psychoses, and normal mood states during the postpartum period.

Thyroid hormones Postpartum depression of late onset has been attributed to thyroid disturbances. Thyroxine, which is high during the third trimester, decreases gradually as thyroid-stimulating hormone (TSH) from the pituitary diminishes after childbearing. After two or three weeks the declining thyroxine reaches a serum level near that of prepregnancy. The drop in thyroxine continues past the prepregnancy level and through a symptom threshold level in some cases. Depressive symptoms are frequent in hypothyroidism and myxedema. Somatic symptoms and signs characteristic of postpartum depression—including diminution of energy, peripheral edema, loss of hair, amenorrhea, and loss of sexual responsiveness—may also occur.

HISTORY The clues that support the foregoing thyroid hypothesis began to accumulate during the 19th century. Marcé reported a host of physical signs and symptoms in cases of depression of late onset, especially those that failed to recover quickly. He made the astute observation that the physical symptoms tended to precede the psychological symptoms. The medical condition of myxedema had not been explored in Marcé's time.

As early as the 16th century, a variety of mentally retarded, edematous dwarfs were reported to live in some of the valleys of the Swiss Alps. Some said that the creatures were the result of the mating of animals with maidens. Others insisted that the dwarfs were the progeny of human fathers and mothers; the dwarfs were human. In the local dialect "Christian" was synonymous with "human," so the dwarfs were called *crestin*. French physicians translated the designation of the dwarfs to "cretin," but not until the second half of the 19th century was it known that the dwarf owed a bizarre body and mental deficiency to a deficit of iodine in the Swiss valleys.

The occurrence of thyroid deficit as a sequel to pregnancy was first noted by the British physician William Withey Gull in 1874. The condition was briefly known as Gull's disease, but the surgeon William Miller Ord insisted that a descriptive term, myxedema, be used. (In *myxedema* a sticky, clear mucuslike fluid exudes when the edematous skin is punctured.) Ord prevailed, since he was chairman of a committee of the Clinical Society of London assigned to study the condition. The committee's report, published in 1883, described 109 dwarfs, 94 of whom were females. Half of the dwarfs had severe psychiatric disorders, described as melancholia, mania, and dementia. Insomnia and occipital headaches were frequent. Of the women, nearly all dated their illness to childbirth.

By the late 1890s biologically active desiccated thyroid became

available, and a host of papers reported on trials of the new medication for many disorders. In 1901 an investigator summarized 42 reports on the administration of thyroid to a total of 638 patients who had myxedema and psychiatric symptoms for many years. Overall 50 percent were reported as recovered, with the investigator noting that patients resistant to treatment were those who had been ill for a long time. A wide range of psychiatric symptoms were reported to be benefited or cured. The most common symptoms were chronic depression and a stuporous condition the investigator described as that of a hibernating animal. Other frequent syndromes were delirium, hallucinations, flight of ideas, delusions, and dementia.

Thus, at the turn of the century, associations between childbearing, thyroid deficit, and psychiatric illness had been discovered. Nevertheless, dominant psychiatric thinking resisted and continues to resist the notion that postpartum diminution of serum thyroxine may be an important factor in postpartum psychiatric illness. A few physicians accidentally discovered the thyroid connection. In 1910 an investigator reported on a case with dramatic relief of postpartum depression after childbirth, and another clinician used thyroid extensively for depression of mood with loss of energy, diminished sexual responsiveness, and insufficient lactation. James Alexander Hamilton in the 1960s reported on the apparently successful use of thyroid in 29 cases of postpartum depression, later extended to more than 200 cases. When triiodothyronine was made available in 1957, it was seen as an opportunity to achieve a thyroid effect quickly and thereby facilitate controlled experimentation with postpartum depression. However, when that approach was attempted in a double-blind study, the rapid changes in mood between drug administration and placebo administration resulted in unacceptable suicidal hazards.

THYROID HORMONE DEFICITS Serum thyroxine, markedly elevated at the end of the third trimester, falls after delivery. On average it reaches and crosses the prepregnancy level three weeks postpartum, but there are individual differences. Recently, work suggests that some women with autoimmune thyroiditis may exhibit a postpartum peak, but that peak is followed by a drop in serum thyroxine. Ten percent of women have postpartum hypothyroidism peaking at four to five months postpartum; the extent of the hypothyroidism can be predicted by the measurement of thyroid antibodies early in pregnancy. The postpartum fall in thyroxine may pass through a threshold of symptom vulnerability to produce the physical and depressive symptoms noted more than 100 years ago.

Thyroid disturbances, particularly hypothyroidism and blunted TSH responses to thyrotropin-releasing hormone (TRH), tend to occur late, rather than early, in the course of postpartum mood disturbances. Large-scale studies examining sensitive thyroid tests in patients most likely to show disorders—that is, patients with late-onset major postpartum depression—are indicated. The limits of being able to do such studies, however, are apparent.

Other biological hypotheses Other hormonal systems that have been implicated in the pathophysiology of postpartum mood disorders but that are too premature to serve as the basis of treatment strategies include prolactin, tryptophan, beta-endorphin, oxytocin, and such neurotransmitters as norepinephrine, dopamine, and serotonin. In view of the disruption of normal daily and biological rhythms with the birth of an infant, consideration of chronobiological hypotheses and treatment strategies are in order and are currently under experimental investigation.

PSYCHOSOCIAL FACTORS Like other medical and psychiatric illnesses, postpartum psychiatric disorders can exacerbate under stress. The disruption of the mother's previous lifestyle and the strain the child can place on the marital relationship constitute significant stressors. However, the clinician should not regard stress alone as a precipitant to the major postpartum psychiatric disorders. Unfortunately, cases of postpartum psychoses have occurred after well-meaning physicians told their patients to reduce the stress in their lives to prevent the onset or the exacerbation of postpartum mood problems. As large-scale epidemiological studies have suggested, women who have significant stressors, such as those who are unmarried or who are from poor socioeconomic backgrounds, do not have higher than usual rates of postpartum psychiatric disorders. A history of infertility may be a risk factor. Particularly in the United States, the lack of an extended family in the home or nearby may precipitate a sense of isolation in the new mother, exacerbate her symptoms, and keep her from getting the help and the support she needs to care for a new infant. Such isolation can also inhibit the early recognition and treatment of postpartum mood disorders by a mental health professional. Psychological precipitants that can aggravate symptoms can be averted by sending a health care worker into the home, a custom endorsed in the United Kingdom. Psychodynamic theories—although they may be helpful, for example, in understanding the need for perfectionism in the mother and the resulting anxiety when perfection is inevitably thwarted by the child—do not provide encompassing explanations for the range, the domain, and the course of symptoms that are currently thought to have a predominantly hormonal cause.

Psychoanalytic explanations for postpartum depressions include a narcissistic loss of the independent self, which must now provide nurturance, rather than be the sole recipient of it. The loss of pregnancy is seen as a loss of closeness with the fetus and may be reminiscent of the loss of some other family member or loved one. In those cases the mother sees the baby as a version of herself. The shift of attention from the mother as a child to her being the source of comfort and gratification contributes to a sense of loss, deprivation, and fatigue. In delusional states the baby is seen as someone else, perhaps a sibling or a lost person with whom the mother shared an ambivalent relationship. Ambivalence in the relationship of the mother to her own mother may also be stimulated during the postpartum period, irrespective of the sex of the child. The infant may engender fantasies, meanings, dependency, and loss issues not unique to the particular mother-infant dyad. In psychoanalytic thinking, obsessional thoughts to hurt the child may derive from previously unacknowledged hostility feelings within the self that were not able to be tolerated by the self concept. Such psychoanalytic concepts have more bearing on the nonpsychotic depressions in the postpartum period than on the spectrum of psychotic postpartum psychiatric disorders, which warrant biological understanding and treatment.

PREDISPOSING FACTORS Primiparous women, women with personal or family histories of mood disorders, and women with previous episodes of depression or psychosis after childbirth are at higher than usual risk for the disorder. Large-scale epidemiological studies do not show that breast-feeding women versus nonbreast-feeding women show different incidences of postpartum psychiatric illness, although there are anectodal reports of women having more than usual mood disturbances after the cessation of breast feeding. Generally, studies show that obstetric variables (length of gestation or delivery, whether vaginal or cesarean, birth weight, dystocia) do not correlate with postpartum psychiatric problems. Obviously, perinatal death is a major loss and, thereby, a cause of depression in the mother, but that depression has a different cause and a different course than hormonally mediated postpartum psychiatric syndromes.

DIAGNOSIS AND CLINICAL FEATURES

Postpartum mood syndromes are listed, along with their clinical features and courses, in Table 15.4-2.

POSTPARTUM PSYCHOSIS The most severe postpartum disorder is an agitated, highly changeable psychosis that develops usually between the 3rd and the 14th day postpartum. The disorder may begin with confusion, depersonalization, and insomnia and then move rapidly to delirium, with prominent hallucinations and transitory delusions. The changeability is marked, so that the term "mercurial" has been applied to the

TABLE 15.4-2
Postpartum Mood Syndromes

	Frequency (all deliveries)	Clinical Features	Course
Maternity blues	50–80%	Crying Irritability Euphoria	3–10 days postpartum
Postpartum depression	10–15%	Melancholia Neurasthenia Insomnia (↓ stage 4 sleep)	80% have onset within six weeks postpartum (not before third postpartum day) Duration: 6–9 months
Postpartum psychosis	0.1%	90% mood disorders 40% mania Core schizophrenic symptoms absent Delirium, confusion	Acute onset within two weeks postpartum Good prognosis Duration: 2–3 months

psychosis. Syndromes may change rapidly. A manic state may appear to clear, only to be followed by a deep depression, which may continue for several days or weeks, followed by recovery or gradual evolution into a moderate depression. The course may be punctuated by occasional outbursts of florid psychosis. Eventually, after weeks or months, the disorder may clear.

Mrs. A was the 32-year-old wife of a physician. She had no personal or family history of psychiatric illness. She had been in good health, and there had been no complications during her pregnancy or delivery. She and her husband had planned for and been looking forward to the birth of their first child. There were no reported major life stressors. The four-year marital relationship was described as stable, and Mrs. A's husband appeared to be supportive.

One week postpartum Mrs. A began to be agitated and confused at certain times of the day. She said to her husband at one point that she had given birth to twin baby girls, rather than a baby boy. Those symptoms disappeared at other times of the day, and Mrs. A appeared to be perfectly normal. The patient was given haloperidol (Haldol), 2 mg at bedtime. Within one week her agitation and delusional symptoms resolved. The patient was followed at weekly intervals for six weeks before the medication was withdrawn. The patient continued to do well but was followed closely throughout the remainder of the postpartum period. Had her symptoms not been treated in their early stages, more severe consequences might have followed.

Informally, the terms "postpartum psychosis" and "puerperal psychosis" are applied to the disorder. The author has suggested that it be called "postpartum psychotic depression" to identify the depressive component. The initial risk for a postpartum psychosis is 1 in 500. However, once a woman has had an episode of postpartum psychosis, her risk for another psychotic episode after a subsequent delivery is about 1 in 3. It appears that women do not develop a tolerance for the disorder; rather, the course of the illnesses appears to obey the model of kindling and behavioral sensitization in that untreated episodes may become more severe and occur spontaneously with increasing frequency over time. One of the most unfortunate consequences of the disorder is that about 4 percent of women with a postpartum psychosis (not depression alone without psychosis) may commit infanticide. Thus, postpartum psychosis is the most severe of the postpartum psychiatric syndromes not only because of the nature of its symptoms but also because, if not recognized early and treated appropriately, it is likely to recur in the future and have potentially devasting consequences for the infant, the mother, her family, and society.

POSTPARTUM DEPRESSION The second postpartum disorder is a moderate to severe depression that begins insidiously after the second or third week postpartum, develops slowly for weeks or months, and then reaches a plateau or improves. The disorder is unofficially called "postpartum depression." The author has suggested "major postpartum depression." A common characteristic of the disorder is the frequency of somatic complaints, especially excessive fatigue. Studies generally indicate that the incidence of postpartum depression is approximately 10 to 15 percent. The disorder may not become apparent until the fourth or fifth month postpartum (the peak incidence of postpartum hypothyroidism) and thus may be missed or at least not attributed to the postpartum state. The risk of developing a postpartum psychosis or depression may continue for a year or, according to some investigators, up to two years postpartum.

Mrs. B was a 36-year-old previously employed primipara with no personal or family history of mood disorders, but she had a father with alcoholism. No problems were reported during the planned pregnancy, and the delivery was uncomplicated. On the fifth day postpartum the patient reported feeling anxious, shaky, and jittery. Over the next week to 10 days, the symptoms progressed until she felt she could not sit still. She had trouble sleeping, and she lost her appetite. She had never had symptoms like those before. She complained of episodes, lasting 1½ to 2 hours, characterized by tightness in her chest, palpitations, and shortness of breath—all associated with a sense of doom.

Her family physician prescribed lorazepam (Ativan) 1 mg as needed. After she had used it for a week, it was deemed not appropriate to continue the medication. Since she was also describing symptoms of depersonalization, she was given perphenazine (Trilafon) 4 mg for sedation and nortriptyline (Aventyl, Pamelor) 50 mg at bedtime for what was seen as an anxious, agitated depression. Her agitated symptoms resolved over the next two weeks. The periphenazine was subsequently withdrawn. The patient appeared to stabilize, but about the third month postpartum the symptoms of a retarded depression began to appear. The nortriptyline dosage was increased to 75 mg to obtain values in the upper range of therapeutic levels. Her depressive symptoms improved. She still noted her increased vulnerability to daily stressors. Therapeutic strategies were discussed and developed to help her get help in the home and to decrease her sense of isolation. She joined a support group and started addressing her own issues of perfectionism and control, derived from her alcoholic family background, that were being frustrated by the inevitable chaos resulting from having an infant in the home. At almost a year postpartum she was dealing with the issues of returning to work, her mood was stabilized, and she felt that she had a good support structure behind her to deal with the added stressors and vicissitudes of returning to the work force. She felt that she could not have addressed the work issues, as well as the home issues, before that time.

That case illustrates how postpartum psychiatric syndromes can initially present with anxious, agitated features resembling a panic disorder and then progress to a retarded depression later in the postpartum course. It also points to the need for longitudinal follow-up in patients. Often, the dynamic issues present themselves and the patients are ready to deal with those issues only after the acute symptoms are treated with pharmacological measures.

MATERNITY BLUES Postpartum major depressive disorder and psychosis need to be distinguished from a condition known as the maternity blues or baby blues, which is not considered to be a disorder; it does not impair functioning, and it occurs in a majority of women. The maternity blues may occur in 50 to 80 percent of women. The condition is characterized by crying, irritability, rapid mood shifts, and even euphoria; it generally appears after the third day postpartum and usually resolves spontaneously within a week. Education and reassurance are

indicated, rather than pharmacological treatment, which is generally not needed unless the condition develops subsequently (but rarely) into a severe disorder.

Mrs. C returned home after the delivery of her first child. Her husband was concerned because she would burst into tears at the drop of a pin. He had previously known her to be sound, stable, and not prone to outbursts. He knew how much she had looked forward to the birth of their child, so he could not understand why she would suddenly get upset. She would say that nothing was bothering her and that she did not know why she was tearful. At times, she appeared to be perfectly happy—in fact, unusually boisterous and euphoric. At other times, she would get irritable over the least little things.

The patient and her husband were given reassurance and education that hers was a normal reaction and that it would most likely resolve on its own over the course of the next week to 10 days, which it did.

DIFFERENTIAL DIAGNOSIS

Although postpartum psychiatric disorders are predominantly mood disorders, they may manifest in a variety of clinical syndromes. They may appear as anxiety disorders, obsessive-compulsive disorders, rapid-cycling mood disorders or cyclothymia, schizophreniform disorders, and such organic disorders as Cushing's syndrome and hypothyroidism, which may present as a delirium. The key to making the diagnosis is recognition of the onset and the course of symptoms having their onset within the first 12 months postpartum.

COURSE AND PROGNOSIS

Postpartum psychosis usually has its onset within the first two weeks postpartum. If treated early and aggressively, it generally has a good prognosis. It may develop into a depression later in its course during the postpartum period. Like psychosis, postpartum depression has a good prognosis with early recognition and treatment, although its onset may be more insidious than postpartum psychosis and not appear until the third or fourth month postpartum. If left untreated, both postpartum depression and postpartum psychosis may become chronic and refractory to treatment, extend into the second and third year postpartum, and cause significant impairment, morbidity, and even mortality.

TREATMENT

A rational treatment plan for postpartum depression and postpartum psychosis cannot be developed from double-blind, placebo-controlled crossover trials of pharmacological or psychotherapeutic interventions. Because the illnesses can be devastating to the mother and her family, clinicians have used whatever interventions have been immediately useful and available. In the literature the majority of the scientifically rigorous treatment studies are confined to studies of patients with maternity blues—that is, women without severe disorders. By necessity, suggested treatment approaches discussed here reflect clinical experience more than information derived from research investigations.

The first principle of treating postpartum depression and postpartum psychosis is that organic illnesses must be ruled out. An initial presentation of postpartum psychiatric illness may be due to an underlying Sheehan's syndrome, thyrotoxicosis (if presenting as an acute psychosis in the first month after delivery), or hypothyroidism (if presenting as a major depression in the fourth or fifth month postpartum). All too often those medical emergencies are overlooked, with disastrous consequences. One of the first crucial steps in the initial evaluation and treatment of postpartum disorders, as in other medical and psychiatric disorders, is a thorough history, physical examination, and laboratory tests.

The other important principle guiding treatment is that the earlier the symptoms are recognized and treated, the better. For example, postpartum psychosis may initially present with symptoms of depersonalization: the patient may feel distant from her child and from the situation at hand. She may feel that she is just an onlooker (portrayed in the film "Rosemary's Baby"). The phenomenon may be interpreted as a failure to bond, but it more likely represents the initial presentation of an emerging psychosis. Patients may then have strange and bizarre sensations or may think that the child's head is separate from the baby's body. If treatment is instituted with small doses of an antipsychotic medication, the symptoms may resolve without a few days or a week. However, if not recognized and treated in its initial stages, the symptoms may rapidly progress to paranoid delusions and a frank agitated psychosis, which may become severe, refractory to treatment, and likely to recur over the next six months to a year. Without aggressive management and early detection, the symptoms may extend into the second and third years postpartum.

Because of the changing nature of postpartum psychiatric illness, different treatments at different stages of the illness are indicated. For example, an early presentation of psychosis is best treated with antipsychotic medication. However, the psychosis may resolve, and the patient may then have symptoms of major depression that require antidepressant medication. Furthermore, the initial presentation of the depression may appear in an agitated form, with many anxious features and insomnia. Then treatment with a sedative antidepressant, such as imipramine (Tofranil), is indicated, whereas later the patient may present with symptoms of a retarded, anergic depression, sometimes with obsessive-compulsive features, in which an activating or serotonergic compound, such as fluoxetine (Prozac), may be indicated. Different treatment modalities may have differential effects and efficacies, depending on when in the course of the illness those treatments are administered.

POSTPARTUM PSYCHOSIS One of the most important aspects of the management of postpartum psychosis is that the earlier it is recognized and treated, the more likely it is to respond to treatment and to have a positive outcome and prognosis. Since most postpartum psychoses have an onset within the first two weeks postpartum (generally not until after the third postpartum day) and 80 percent of them occur within one month postpartum, clinicians should be on the alert for early signs of depersonalization, delusional thinking, mania, or bizarre behavior, especially if the woman has a previous history of postpartum psychiatric illness or a mood disorder. The clinician should hospitalize any patient with symptoms of an impending postpartum psychosis. Early hospitalization can prevent infanticide and suicide, which may occur when mothers at risk are left alone at home to care for their infants.

Often, small (2 to 5 mg) doses of antipsychotics—such as haloperidol or, if that is too potent, perphenazine or loxapine (Loxitane)—may decrease the symptoms and prevent the development of a severe psychosis.

If the symptoms of an emerging postpartum psychosis are recognized and treated early, they may resolve within a week. Cases in which the symptoms are not recognized and treated in their initial stages may become refractory to treatment and take a long time to resolve. In general, however, the postpartum

psychoses have a good prognosis, resolve in two to three weeks, and are amenable to treatment. Postpartum psychosis is the condition under which women are most likely to commit infanticide; an estimated 4 percent of women with postpartum psychoses commit infanticide. That consequence generally does not occur unless the woman is psychotic. The tragedy is made all the more poignant by the recognition that the disorder is otherwise amenable to treatment, and the tragedy is, thereby, preventable.

Although dosages of antipsychotics can be reduced after the initial episode of psychosis is resolved, the reduction should be done gradually and cautiously. Women remain at risk for recurrences, particularly those women with a previous history of psychiatric illness, for at least 6 months and sometimes up to 12 months postpartum. Data from a large-scale epidemiological study in Edinburgh, Scotland, suggest an increased risk for psychiatric admissions for up to two years postpartum. Although the clinician need not maintain a patient on antipsychotic medication for that length of time, the clinician should be on the alert for early signs of recurrence and should remember that a patient who initially presents with symptoms of a postpartum psychosis within the first few weeks after delivery may have symptoms of a postpartum depression later in the course of her illness—for example, four or five months postpartum. In an early onset of psychoses, patients should probably continue to take antipsychotics for at least six weeks postpartum. Antipsychotics are not contraindicated with breast feeding.

As in other psychiatric illnesses, postpartum psychosis responds best to psychopharmacological measures when they are combined with psychotherapeutic interventions. Pharmacological intervention is urgently needed to keep the mother from becoming increasingly psychotic and committing infanticide. At that point the patient is not cognitively and emotionally available to participate in a psychotherapeutic interaction until the medications reduce the hallucinations, delusions, and agitated behavior. However, as most clinicians and even psychotic patients appreciate, medications are most likely to be received and taken willingly when the patient and her family perceive some sense of rapport, trust, and support from the physician.

POSTPARTUM DEPRESSION In contrast to postpartum psychosis, which has an onset early in the postpartum period, postpartum depression generally has an insidious onset that may occur later, such as four to five months postpartum, and may range from mild to moderate dysthymia and anxiety disorders to major melancholia. As with the postpartum psychoses, organic abnormalities—particularly hypothyroidism, which occurs in 10 percent of women postpartum, with a peak incidence at four to five months—need to be ruled out. Transient hyperthyroidism may appear early in the postpartum course. Indications for the use of antidepressant medication are similar to those for other mood disorders and include the presence of neurovegetative signs. Untreated episodes tend to become severe, frequent, and often refractory to treatment. The depressive episodes should be treated aggressively with both pharmacological and psychotherapeutic strategies early in the course to prevent untoward biological and psychological consequences. Since many of the depressions may appear with obsessive-compulsive features, implicating serotonergic mechanisms, recent clinical experience suggests the efficacy of the serotonergic antidepressants, such as fluoxetine. However, side effects, particularly agitation, need to be monitored closely, and fluoxetine should not be the first line of treatment in the anxious depressions often seen early in the postpartum state.

For patients who present with symptoms of agitated and anxious depressions, such sedative antidepressants as imipramine are appropriate. If agitated depressive symptoms occur early in the postpartum state, small doses of antipsychotics can be beneficial. Anxiolytics are best avoided because of their risk for the development of physiological dependence, withdrawal, and exacerbation of agitation and because of their inadvisability for use in breast-feeding women. When using an antidepressant, the clinician should advise the woman to stop breast feeding, as some studies indicate that small amounts of the drug may be excreted into the breast milk. If administering antidepressant drugs to a postpartum patient, the clinician should rule out hypothyroidism, closely follow the course and the timing of the patient's mood changes, and discontinue the antidepressant if the woman shows evidence of drug-induced rapid cycling. In the potentially hypothyroid postpartum state, antidepressants may induce rapid cycling and are not recommended in breast-feeding women. Being female, being in the postpartum state, and being hypothyroid are all risk factors for tricyclic-induced rapid cycling.

Recently, estrogen skin patches have been reported to be beneficial in severe postpartum depression. For postpartum dysphoria one investigator has recommended progesterone treatment (100 mg intramuscularly [IM] for the first postpartum week and then 400 mg twice a day by suppository for two or more months postpartum). However, some clinicians and investigators find that progesterone may exacerbate depression.

For severe or psychotic postpartum depression or mania refractory to pharmacotherapy, electroconvulsive therapy (ECT) remains the treatment of choice. Sleep deprivation has therapeutic efficacy in a majority of patients with major depressive disorders. The efficacy of sleep deprivation in postpartum mood disorders is currently under experimental investigation. The relapse that may occur after sleep deprivation may be averted with lithium.

Since the experience of a postpartum depression can be cognitively and emotionally disruptive for the woman and her family, the disorder, like other psychiatric disorders, is best treated with a combination of pharmacological and psychotherapeutic management. The clinician should provide education, support, and cognitive structuring so that the patients and their families can find some method out of the madness that stems from the confusing, disorienting, and emotionally traumatic cataclysm in their lives.

Anthropological studies indicate that other cultures have rituals allowing for 40-day rest periods for the mother after the birth of a baby in which to mother the mother. During that time period, the focus is on allowing the mother time to rest, recuperate, eat, and sleep. Female relatives come to the home to prepare meals, do housework, and care for the infant. Thus, social support, education, child care services, and social recognition of the new motherhood status is ensured. In this country in the past a one-week hospital stay for the mother was required after delivery. Now, the mother usually goes home a day after delivery and often without an extended family or neighbors to help with infant care. In that isolated environment, the woman does not receive the supportive therapeutic factors that would help mitigate the development or the exacerbation of a spectrum of nonpsychotic depressions.

MATERNITY BLUES As mentioned earlier, the maternity blues is not considered a disorder, since it occurs in 50 to 80 percent of women and because of the absence of major symptoms. The blues is best treated with reassurance that the symp-

toms occur in a majority of women and that they generally improve spontaneously in a week to 10 days. In rare instances the symptoms may progress to a severe postpartum disorder, a fact that stresses the necessity of making frequent follow-up visits. However, that progression is the exception, rather than the general rule.

In contrast to postpartum psychosis, pharmacological intervention is generally not warranted for the maternity blues. Instead, psychotherapeutic intervention in the form of education, support, and reassurance is needed.

PROPHYLAXIS Since there is a high recurrence rate for both postpartum psychosis (initial risk, 1 in 500; recurrent risk, 1 in 3) and postpartum depression (initial risk, 1 in 10; recurrent risk, 1 in 2), prophylactic treatment for women, particularly for those who have a previous history of mood disorders, is an integral part of the management of the disorders.

Patients with a previous history of nonpuerperal mood disorders are three times more likly to have postpartum mood disorders, particularly mania, than are women who had no history of mood disorders. One of the most effective prophylactic interventions is lithium. Although lithium dosage should be halved about one week before delivery because of marked fluid and electrolyte changes occurring in the woman then, it can be restarted shortly after delivery. However, lithium, in contrast to antipsychotic medication, is contraindicated in breast-feeding women. Clinicians should be particularly alert for lithium-induced hypothyroidism in postpartum women, since 90 percent of lithium patients with hypothyroidism are women and since the postpartum period presents a particular risk factor for the development of hypothyroidism. Furthermore, postpartum hypothyroidism may induce rapid mood cycling.

Patients with a previous history of mood disorders may have an exacerbation of their illness during pregnancy. Although lithium is contraindicated during the first trimester because of the infant's risk for Ebstein's anomaly of the heart, in severe cases lithium may be administered cautiously, checking particularly for fluid and electrolyte changes in the woman, during the third trimester. For mania occurring during pregnancy, antipsychotics or ECT can be given without undue risk to the fetus.

Another prophylactic treatment that has received attention, although it is controversial, is progesterone (100 mg IM after labor, daily for seven days, then progesterone suppositories for two months or until the return of menstruation). Since progesterone is essentially an anesthetic in animals, its use in humans is probably more effective for the agitated than for the depressive symptoms of postpartum psychiatric syndromes. It may exacerbate depressive symptoms.

One additional body of information supports the hypothesis that postpartum illnesses are unique and organic in cause: reports of the successful use of three different substances for prophylaxis in high-risk patients—that is, patients who have had previous postpartum psychoses or depressions. The three substances are long-acting parenteral estrogen, long-acting progesterone, and pyridoxine, although lithium prophylaxis is at present the mainstay of treatment for recurrent mood disorders.

SUGGESTED CROSS-REFERENCES

Further information on the reproductive endocrinology of pregnancy and the postpartum period and guidelines for the use of psychotropics during pregnancy and lactation can be found in Section 29.4 on psychiatry and reproductive medicine. Mood disorders are discussed at length in Chapter 16, and brief psychotic disorder is discussed in Section 15.1.

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CHAPTER 16 MOOD DISORDERS

16.1 MOOD DISORDERS: INTRODUCTION AND OVERVIEW

HAGOP S. AKISKAL, M.D.

PRESENT SCOPE OF MOOD DISORDERS

PUBLIC HEALTH SIGNIFICANCE Known for nearly 2,500 years, mood disorders continue to command major public health interest. Especially in their depressive forms, they are among the most common maladies, affecting at least 12 percent of women and 8 percent of men at some time during life. Those figures are extrapolated from the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area studies performed in five sites in the United States. Despite the availability of effective treatment, many persons with mood disorders are disabled, and rates of suicide, a complication occurring in about 15 percent of depressive disorders, are high in young and, especially, elderly men. Thus, although depressive disorders are more common in women, more men than women die of suicide.

The epidemiological trends cannot be ascribed to underdiagnosis and undertreatment alone. The arguments are several. First, Gerald Klerman and colleagues suggest that the incidence of mood disorders may be increasing in younger age groups, especially in cohorts born in the 1960s, and may be associated with rising rates of alcohol and substance abuse. Second, mood disorders, once believed to be essentially adult disorders, are increasingly diagnosed in children and adolescents. Third, clinical studies suggest higher rates of chronicity, recurrence, and refractoriness than previously believed. For instance, chronicity, reported by Emil Kraepelin to be no more than 5 percent at the turn of the century in Germany, is now seen in about 15 percent of cases of mood disorders in Western countries.

BROADENING THE BOUNDARIES OF MOOD DISORDERS Current conceptualization of mood disorders in the United States embraces a wide spectrum of disorders, including many conditions previously diagnosed as schizophrenia, personality disorder, or neurosis. The diagnostic shift occurred in part as a result of the United States-United Kingdom Diagnostic Project, which demonstrated that schizophrenia was being diagnosed at the expense of mood disorders (Figure 16.1-1). The broadening of the conceptual boundaries was further stimulated by the availability of new and effective treatments, both somatic and psychotherapeutic, and by the high risk for tardive dyskinesia and suicide in persons with mood disorders incorrectly given other diagnoses. Present research interest in mood disorders emanated from a landmark NIMH conference on the psychobiology of affective illnesses, published in 1972. The NIMH Collaborative Depression Study—a long-term prospective project deriving directly from recommendations made at the conference—has legitimatized the broader perspective. Nevertheless, current data (summarized by Martin Keller and collaborators) suggest widespread undertreatment of mood disorders.

In Europe, where the concept of mood disorders has historically embraced a broad spectrum of disorders, the work of two British schools of thought has been influential. The Maudsley school—Aubrey Lewis and his followers—has promoted a continuum model from anxiety disorders to mild neurotic depressions to severe endogenous and psychotic depressions, whereas the Newcastle school, led by Martin Roth, has sharply demarcated those conditions from one another. Although vestiges of both approaches are still influential in clinical and basic research, their significance seems overshadowed by continental European studies that subdivide mood disorders on the basis of polarity: unipolar (depressive episodes only) and bipolar (depressive episodes plus manic or hypomanic episodes). That subdivision, supported by studies in the United States, has served as the basis for much recent research into and classification of mood disorders, as reflected in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and the 10th revision of the *International Classification of Diseases and Related Health Problems* (ICD-10).

CONCEPTS AND DEFINITIONS

Mood disorders encompass a large group of psychiatric disorders in which pathological moods and related vegetative and psychomotor disturbances dominate the clinical picture. Known in previous editions of DSM as affective disorders, the term "mood disorders" is preferred today because it refers to sustained emotional states and not merely to the external (affective) expression of the present emotional state. Mood disorders are best considered as syndromes (rather than discrete diseases) that consist of a cluster of signs and symptoms that are sustained over a period of weeks to months, represent a marked departure from a person's habitual functioning, and tend to recur, often in periodic or cyclical fashion.

MAJOR DEPRESSIVE DISORDER AND BIPOLAR DISORDERS Major depressive disorder, sometimes called unipolar depression (not a DSM-IV term), is the most common mood disorder. It may manifest as a single episode or as recurrent episodes. The course may be somewhat protracted—up to two years or longer—in those with the single episode form. Whereas the prognosis for recovery from an acute episode is good for most patients with major depressive disorder, two out of three patients experience recurrences throughout life, with varying degrees of residual symptoms between episodes.

Bipolar disorder, previously called manic-depressive disorder (not a DSM-IV diagnosis), consists of at least one excited (manic or hypomanic) episode; although some patients experience only manic episodes, most end up having one or more depressive episodes. During the numerous recurrences of the

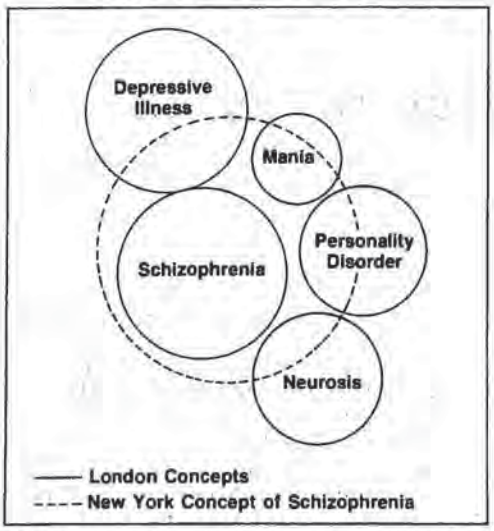

FIGURE 16.1-1 *Comparison of British (London) and United States (New York) concepts of schizophrenia. (Figure from J E Cooper, R E Kendell, B J Garland, L Sharpe, J R M Copeland, R Simon:* Psychiatric Diagnosis in New York and London. *Oxford University Press, London, 1972. Used with permission).*

alternating or cyclical phases, about one third of patients also develop mixed states, comprising simultaneous depressive and manic symptoms. The bipolar disorders were classically described as psychotic mood disorders with both manic and major depressive episodes (now termed bipolar I disorder), but recent clinical studies have shown the existence of a spectrum of ambulatory depressive states that alternate with milder and short-lived periods of hypomania rather than full-blown mania (bipolar II disorder). Those subdivisions within the larger group of bipolar disorders have focused attention on the entire range of bipolar disorders. Bipolar II disorder, which is not always easily discriminable from recurrent major depressive disorder, illustrates the need for more research to elucidate the relationship between bipolar disorders and major depressive disorder.

CYCLOTHYMIC DISORDER AND DYSTHYMIC DISORDER Clinically, it is observed that major depressive episodes often arise from low-grade intermittent or chronic depression known as dysthymic disorder. Likewise, many instances of bipolar disorders, especially ambulatory forms, represent episodes of mood disorder superimposed on a cyclothymic background, that is, numerous brief periods of hypomania alternating with numerous brief periods of depression. Dysthymia and cyclothymia were two of the basic temperaments described by Kraepelin and Ernst Kretschmer as predisposing persons to affective illness. Cyclothymic disorder and dysthmic disorder frequently coexist with borderline personality disorder.

It is not always easy to demarcate full-blown syndromal episodes of depression and mania from their subsyndromal temperamental counterparts commonly observed during the interepisodic periods. The subsyndromal episodes appear to be fertile ground for interpersonal conflicts and postaffective pathological character developments that may ravage the lives of patients and their families. In North America many such patients end up being labeled with borderline personality disorder.

Cyclothymic disorder and dysthymic disorder also exist in the community as subaffective disorders without progression to full-blown mood disorder episodes. However, at least one out of three persons with those disorders does make the transition to a major mood disorder. Understanding the factors that mediate the transition is important for preventing manic and depressive episodes.

COMORBID DISORDERS Mood disorders, especially depressive disorders, overlap considerably with anxiety disorders. As summarized in an NIMH monograph edited by Jack Maser and Robert Cloninger, anxiety disorders can occur during an episode of depression, may be a precursor to the depressive episode, and, less commonly, may occur during the future course of a mood disorder. Those findings suggest that at least some depressive disorders share a common diathesis with certain anxiety disorders. Other NIMH epidemiological research indicates that comorbidity of mood (especially bipolar) disorder and substance and alcohol abuse is common. In some cases the alcohol or substance abuse may represent an attempt at self-treatment of the mood disorder. Finally, physical illness—both systemic and cerebral—occurs in association with mood disorders with a frequency greater than would be expected by chance alone.

NEED FOR CLINCAL INTEGRATION Research on comorbid conditions is in early stages and is not further elaborated in this section. Instead, the discussion focuses on the major conceptual developments that have shaped current views of mood disorders and have contributed to an integrative pathogenetic framework that takes into account the interactions of social, psychological, and biological factors as originally formulated by the author and William McKinney in 1973. An integrated framework of pathogenesis is necessary for understanding psychopharmacological, somatic, and psychotherapeutic approaches in the clinical management of patients with mood disorders.

CLASSICAL DESCRIPTIONS OF MELANCHOLIA AND MANIA

Much of what is known today about mood disorders was described by the ancient Greeks and Romans. The terms "melancholia" and "mania" were coined and their relation was noted. The ancients also hypothesized a temperamental origin for those disorders. Much of modern thinking about mood disorders, as exemplified by the work of the French and German schools in the middle and latter part of the 19th century—which influenced current British and American concepts—can be traced back to these ancient concepts.

MELANCHOLIA Hippocrates (460–357 BC) described melancholia ("black bile") as a state of "aversion to food, despondency, sleeplessness, irritability, [and] restlessness." Thus, in choosing the name of the condition, Greek physicians, who may have borrowed the concept from ancient Egyptians, postulated the earliest biochemical formulation of any mental disorder. They further believed the illness often arose from the substrate of the somber melancholic temperament, which, under the influence of the planet Saturn, made the spleen secrete black bile, which ultimately darkened the mood through its influence on the brain. Greek descriptions of the clinical manifestations of depression and of the temperament prone to melancholia are reflected in the DSM-IV and in the subdepressive lethargy, self-denigration, and habitual gloom of the person with dysthymic disorder.

One of the Hippocratic aphorisms recognized the close link between anxiety and depressive states: "Patients with fear . . . of long-standing are subject to melancholia." According to Galen (AD 131–201), melancholia manifested in "fear and depression, discontent with life, [and] hatred of all people." A few hundred years later another Roman, Aurelianus, citing the now lost works of Soranus of Ephesus, amplified the role of aggression in melancholia (and its link to suicide) and described how the illness assumed delusional coloring: "Animosity toward members of the household, sometimes a desire to live and at other times a longing for death, suspicion on the part of the patient that a plot is being hatched against him."

In addition to natural melancholia, which arose from an innate predisposition to overproduce the dark humor and led to a more severe form of the malady, Greco-Roman medicine recognized such nonnatural (environmental) contributions to melancholia as immoderate consumption of wine, perturbations of the soul due to the passions (for example, love), and disturbed sleep cycles. Autumn was considered to be the season most disposing to melancholy.

MANIA A state of raving madness with exalted mood was noted by the ancient Greeks, although it referred to a somewhat broader group of excited psychoses than in modern nosology. Its relation to melancholia was probably noted as early as the first century BC, but according to Aurelianus, Soranus discounted it. Nonetheless, Soranus had observed the coexistence of manic and melancholic features during the same episode, consisting of continual wakefulness and fluctuating states of anger and merriment, sometimes of sadness and futility. Soranus thus seemed to have described what today are called mixed episodes in DSM-IV. Although natural melancholy was generally considered a chronic disorder, Soranus noted the tendency for attacks to alternate with periods of remission.

Although others prior to him hinted at it, Aretaeus of Cappadocia (circa AD 150) is generally credited with making the connection between the two major mood states: "It appears to me that melancholy is the commencement and a part of mania." He described the cardinal manifestations of mania as it is known today:

> There are infinite forms of mania but the disease is one. . . . If mania is associated with joy, the patient may laugh, play, dance night and day, and go the market crowned as if victor in some contest of skill. . . . The ideas the patients have are infinite. . . . [They] believe they are experts in astronomy, philosophy, or poetry. . . .

Aretaeus described the extreme psychotic excitement that could complicate the foregoing clinical picture of mania:

> The patient may become excitable, suspicious, and irritable. . . . [H]is hearing may become sharp. . . . [S]ome get noises and buzzing in the ears . . . or may have visual hallucinations . . . bad dreams and his sexual desires may get uncontrollable. . . . [I]f aroused to anger, he may become wholly mad and run unrestrainedly, roar aloud . . . kill his keepers, and lay violent hands upon himself.

Noting the fluctuating nature of symptoms in the affectively ill, Aretaeus commented:

> They are prone to change their mind readily; to become base, mean-spirited, illiberal, and in a little time . . . extravagant, munificent, not from any virtue of the soul, but from the changeableness of the disease.

Aretaeus was thus keenly aware of the characterological distortions so commonly manifested during the different phases of cyclical mood disorders.

Finally, consolidating the knowledge of several centuries, Aretaeus described mania as a disease of adolescent and young men given intermittently to "active habits . . . drunkenness, lechery" and an immoderate life-style (what today might be called cyclothymic disorder). Exacerbations were most likely to occur in the spring.

AFFECTIVE TEMPERAMENTS The concept of health and disease in Greco-Roman medicine was based on harmony and balance of the four humors, of which the sanguine humor was deemed the healthiest. But even a desirable humor like blood, which made people habitually active, amiable, and prone to jest, could in excess lead to the pathological state of mania. The melancholic temperament, dominated by black bile and predisposed to pathological melancholia, was described as lethargic, sullen, and given to brooding or contemplation; its modern counterparts are depressive personality disorder and dysthymic disorder. A long tradition dating back to Aristotle (384–322 BC) attributed creative qualities to the otherwise tortured melancholic temperament in such fields as philosophy, the arts, poetry, and politics. The remaining two temperaments, choleric and phlegmatic, were less desirable, as yellow bile made people choleric (irritable, hostile, and given to rage) and phlegm made them phlegmatic (indolent, irresolute, and timid). The choleric and phlegmatic temperaments would probably be recognized today as borderline and avoidant personality disorders, respectively.

Many of the original Greek texts on melancholia were transmitted to posterity through medieval Arabic texts such as those of Ishaq Ibn Imran and Avicenna (and their Latin rendition by Constantinus Africanus). In describing different affective states, Avicenna developed the theory of the temperaments to its fullest. He speculated that a special form of melancholia supervened "if black bile . . . be mixed with phlegm" when the illness was "coupled with inertia, lack of movement, and quiet." Further, mania was not necessarily linked to the sanguine (hypomanic) temperament, as many forms of excited madness were believed to represent a mixture of black and yellow bile. Avicenna further observed that the appearance of anger, restlessness, and violence heralded the transition of melancholia to mania. Those elaborations on Galen's tempermental types might be considered the forerunners of current personality dimensions, deriving mood states from various mixtures of neuroticism and introversion-extroversion. Finally, the speculation on how diverse depressive phenomena could be understood as a mix of humors anticipated modern multiple-transmitter hypotheses of depression.

Ishaq Ibn Imran summarized the existing knowledge of melancholia by considering the interaction of genetic factors ("injured prenatally as the result of the father's sperm having been damaged") with a special temperament given to "mental overexertion"—though not necessarily physical overactivity—and that in turn was associated with "disruption of the correct rhythms . . . of sleeping and waking." Those views, too, have a very modern ring to them.

BEGINNINGS OF MULTIFACTORIAL CONCEPTUALIZATION The first English text (Figure 16.1-2) entirely devoted to affective illness was Robert Burton's *Anatomy of Melancholy*, published in 1621. A scholarly review of two millennia of medical and philosophical wisdom, the text also gives a sufferer's perspective. The concept of affective disorder endorsed by Burton was rather broad—as it always has been in the United Kingdom—embracing mood disorders and many of the disorders today considered somatoform disorders, including hypochondriasis. Although he described "causeless" melancholias, Burton also categorized the various forms of love melancholy and grief. Particularly impressive was his catalog of causes, culminating in a grand conceptualization:

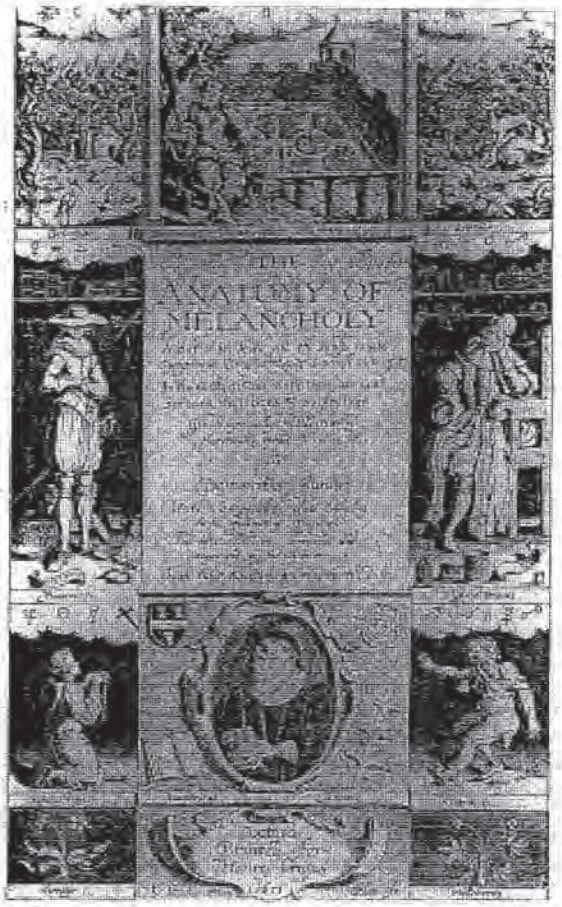

FIGURE 16.1-2 *Frontispiece of Robert Burton's* Anatomy of Melancholy *(1621).*

Such as have . . . Saturn . . . misaffected in their genitures . . . such as are born of melancholy parents . . . as offend in those six non-natural things, are of a high sanguine complexion . . . are solitary by nature, great students, given to much contemplation, lead a life out of action, are most subject to melancholy. Of sexes both, but men more often. . . . Of seasons of the year, autumn is most melancholy. Jobertus excepts neither young nor old. . . .

Burton's six nonnatural things referred to such environmental factors as diet, alcohol, biological rhythms, and perturbations of the passions such as intense love. Burton himself did not definitively indicate age prevalences. Like nearly all of his predecessors, he favored male (rather than the currently reported female) preponderance. Finally, Burton considered both the melancholic (contemplative) and the sanguine (hot-blooded) temperaments to be substrates of melancholia. Burton's work clearly links certain forms of depression with the softer expressions of the manic disposition, or bipolar II disorder.

EARLY MODERN ERA

CONCEPT OF AFFECTIVE DISORDER Although Celsus (circa AD 30) had described forms of madness that go no further than sadness, the French alienist Jean-Philippe Esquirol (1772–1840) may have been the first psychiatrist in modern times to suggest that a primary disturbance of mood might underlie many forms of depression and related paranoid psychoses. Until Esquinol's work melancholia had been categorized as a form of insanity—that is, ascribed to deranged reasoning or thought disturbance. Esquirol's observations on melancholic patients led him to postulate that their insanity was partial—dominated by one delusion, a monomania—and that "the symptoms were the expression of the disorder of the affections. . . . [T]he source of the evil is in the passions." He coined the term "lypemania" (from the Greek, "sorrowful insanity") to give nosological status to a subgroup of melancholic disorders that were affectively based. Esquirol cited Benjamin Rush (1745–1813), the father of American psychiatry, who had earlier described tristimania, a form of melancholia in which sadness predominated.

Esquirol's influence led other European psychiatrists to propose milder states of melancholia without delusions, which were eventually categorized as simple melancholias and, ultimately, as primary depressions. Such descriptions culminated in the Anglo-Saxon psychiatric term "affective disorder." The term was coined by Henry Maudsley (1835–1918), the renowned British psychiatrist after whom the London hospital is named:

The affective disorder is the fundamental fact. . . . [I]n the great majority of cases it precedes intellectual [delusional] disorder. . . . [I]t frequently persists for a time after this has disappeared.

MANIC-DEPRESSIVE ILLNESS AND THE QUESTION OF PSYCHOGENIC DEPRESSIONS Although the connection between mania and depression had been sporadically rediscovered since it was first described 2,000 years ago, the clinical work that finally established "circular insanity" (Jean-Pierre Falret's term) as *folie à double forme* (Jules Baillarger's term) was undertaken by those two Esquirol disciples in the 1850s. That accomplishment built on Philippe Pinel's reforms, which championed the humane treatment of the mentally ill in Paris around the turn of the 18th century and emphasized systematic clinical observations of patients, detailed in case records. French alienists made longitudinal observations on the same patient from one psychotic attack into another. Further, Esquirol had introduced the chronicling of events in statistical tables. Thus, the Hippocratic approach to defining a particular case by its onset, circumstances, course, and outcome was applied by French alienists in studying the affectively ill. The humanitarian reforms introduced in the 19th century ensured that standards of general health and nutrition would improve the outlook for the mentally ill—especially those with potentially reversible disorders like affective disorders—who could now be discharged from the asylums. The French school, then, by segregating the nondeteriorating mood disorders from the dementing types of insanity, paved the way for the Kraepelinian system.

Kraepelin's (1856–1926) unique contribution was not so much his grouping together of all the forms of melancholia and mania, but his methodology and painstaking longitudinal observations, which established manic-depressive illness as a nosological and, he hoped, a disease entity. His rationale was as follows: (1) The various forms had a common heredity measured as a function of familial aggregation of homotypic and heterotypic cases. (2) Frequent transitions from one form to the other occurred during longitudinal follow-up. (3) A recurrent course with illness-free intervals characterized most cases. (4) The superimposed episodes were commonly opposite to the patient's habitual temperament; that is, mania was superimposed on a depressive temperament and depression was superimposed on a hypomanic temperament. (5) Both depressive and manic features could occur during the same episode (mixed states). Kraepelin's synthesis was developed as early as the

sixth (1899) edition of his *Lehrbuch der Psychiatrie* and most explicitly stated in the opening passages of the section on manic-depressive psychosis in the eighth edition (published in four volumes, 1909–1915):

> Manic-depressive insanity . . . includes on the one hand the whole domain of so-called periodic and circular insanity, on the other hand simple mania, the greater part of the morbid states termed melancholia and also a not inconsiderable number of cases of [confusional insanity]. Lastly, we include here certain slight and slightest colorings of mood, some of them periodic, some of them continuously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders, on the other hand, pass over without . . . boundary into the domain of personal predisposition.

For Kraepelin, the core pathology of clinical depression consisted of lowering of mood and slowed (retarded) physical and mental processes. In mania, by contrast, the mood was elated and both physical and mental activity accelerated. Although his earlier observations on what he termed "involutional melancholia" (referring to 40- to 65-year-old patients with extreme anxiety, irritability, agitation, and delusions) had led him to separate that entity from the broader manic-depressive rubric, in the eighth edition of *Lehrbuch der Psychiatrie* he united it with the manic-depressive group with the justification that it was a special form of mixed state.

The classification of depressive disorders is still evolving. Karl Leonhard in 1957, Jules Angst in 1966, Carlo Perris in 1966, and George Winokur, Paula Clayton, and Theodore Reich in 1969, working independently in four different countries, proposed that depressive disorders without manic or hypomanic episodes (major depressive disorder) that appear in middle age and later are distinct from depressive episodes that begin at earlier ages and alternate with manic or hypomanic episodes (bipolar disorder). The main difference between the two disorders is the greater familial loading for mood disorder, especially for bipolar disorder.

Kraepelin had conceded the occurrence of psychogenic states of depression occasioned by situational misfortune. Manic-depressive illness, on the other hand, he believed to be hereditary. Yet he could not document postmortem anatomopathological findings in the brains of manic-depressive patients. Therefore, manic-depression had to be conceptualized as a functional mental disorder in which brain disturbances were presumed to lie in altered physiological functions. Such biological factors were deemed absent in the psychogenic depressions. Thus, Kraepelin's classification of mood disorders is both dualistic and unitary. It is dualistic to the extent that he divided them as either psychologically occasioned or somatically caused. It is unitary with respect to disorders in the latter group, which have been termed endogenous affective disorders (that is, due to internal biological causes). In other words, Kraepelin restricted the concept of clinical depression to what DSM-IV terms "major depressive disorder with melancholic features." Moreover, he postulated a continuum between that condition and what DSM-IV terms "bipolar disorder."

As summarized in Table 16.1-1, in the past century endogenous depressions have been contrasted with those of exogenous cause (that is, external and, presumably, psychogenic causes). Transitions between the two groups are so frequent, however, that the two-type thesis of depression has been largely abandoned in official classifications in North American psychiatry. The endogenous-exogenous dichotomous grouping still has many adherents in the United States, Europe, and elsewhere in the world who continue to research actively its potential for clinical predictions. Those research endeavors generally attempt to validate the various subtypes based on their clinical characteristics rather than presumed etiology. Indeed, most clinical researchers today would probably agree that most forms of depression have endogenous and exogenous etiological components. Consensus would be less likely on how to delimit clinical depressive disorder from potentially comorbid disorders such as the various anxiety disorders, substance use disorders, and personality disorders. Clarifying the boundaries between those disorders has emerged as a principal challenge in the classification of mood disorders.

TABLE 16.1-1
Overlapping Dichotomies of Affective Disorders That Are Not Necessarily Synonymous

Manic-depressive	Psychogenic
S (somatic) type	J (justified) type
Autonomous	Reactive
Endogenous	Exogenous
Psychotic	Neurotic
Acute	Chronic
Major	Minor
Melancholic	Neurasthemic
Typical	Atypical
Primary	Secondary
Biological	Characterological

Cartesian thinking in 17th-century France conceptually separated mind from body, thereby providing physicians autonomy over the somatic sphere, freed from interference by the Church. The dichotomous paradigm ensured that study of the two aspects of the human organism would be unconfounded by the complexities of mind-body interactions. That is one reason why Kraepelin's descriptive observations have proved valuable to subsequent generations of clinicians. Further, his approach exemplifies the best tradition of scientific humanism in medicine: Description and diagnostic categorization of an individual patient are necessary if the physician is to offer the patient the fruits of knowledge gained from past observations made on similarly described and diagnosed patients. One limitation to the Kraepelinian approach is its biological reductionism, as a result of which it is not sufficiently articulate to account for mind-body interactions in the genesis of mental disorders.

DEPRESSIONS AS PSYCHOBIOLOGICAL AFFECTIVE REACTION TYPES Bridging the divide between psyche and soma was the ambition of the Swiss-born Adolf Meyer (1866–1950), who dominated psychiatry from his chair at Johns Hopkins University during the first half of the 20th century. Meyer coined the term "psychobiology" to emphasize that both psychological and biological factors could enter into the causation of depressive disorders and other mental disorders. Because of the nascent state of brain science during Meyer's time, he was more adept at biography than biology and therefore paid greater attention to psychosocial causation. He preferred the term "depression" ("pressed down") to "melancholia" because of its lack of biological connotation. He conceived of depressive states in terms of unspecified constitutional or biological factors interacting with a series of life situations beginning at birth or even at conception. From that viewpoint arose the unique importance accorded to personal history in depressive reactions to life events.

Meyer's terminological revision left a somewhat confusing legacy in that the term "depression" is now applied to a broad range of affective phenomena ranging from sadness and adjustment disorders to clinical depressive disorders and bipolar disorders. Repercussions can be seen in the low threshold for diagnosing major depressive disorder in DSM-IV, which renders difficult the differentiation of major depressive disorder from transient life stresses that produce adjustment disorder with

depressed mood. Nosological nuances to which Meyerians paid little attention, such as the difference between melancholic depression and more mundane depressions, are not just a matter of semantics. To the extent that those two forms of depression are seen in different clinical settings, hypotheses based on one population may not apply to the other. For instance, study subjects may have learned, as a consequence of uncontrollable traumatic events in their biography, to feel helpless or to view the world in a negative light, but that does not equate with clinical illness. Failure to make such nosological distinctions further clouds interpretations of the results of trials of psychotherapy versus pharmacotherapy for depressive disorders.

The Meyerian emphasis on biographical factors and their meaning for the patient represented a more practical approach to depth psychology. Recent sociological interpretations of depression can also be traced to Meyer's work. But in the final analysis the Meyerian concern for the uniqueness of the individual has proved heuristically sterile. It de-emphasizes what is diagnostically common to different individuals, thereby obscuring the relevance of accrued clinical wisdom for the index patient. For that reason the Meyerian approach, after enjoying clinical popularity for several decades in North America, has given way to neo-Kraepelinian rigor. However, the psychobiological vision of bridging biology and psychology, one of the major preoccupations of psychiatric thought and research today, represents a Meyerian legacy.

CONTEMPORARY ETIOLOGICAL MODELS OF DEPRESSION

From classical times through the early part of the 20th century, advances in understanding mood disorders broadly involved conceptual shifts from supernatural to naturalistic explanations, from reductionistic, unitarian theories of causation to pluralistic theories, and from dualism to psychobiology. Knowledge of those conceptual developments provides a useful base from which to scrutinize more recent models and concepts of mood disorder, developed later in the 20th century. The new approaches, derived from competing theoretical positions, have generated models for understanding various aspects of mood disorders, particularly depressive disorders (Table 16.1-2).

The formative influence of early experience as it is dynamically shaped by emerging mental structures during development is the common denominator for the psychoanalytic concepts of psychopathological phenomena. By contrast, behavioral approaches in their more traditional formulations focus on the pathogenetic impact of proximate contexts. The cognitive approaches, which are akin to the behavioral-pathogenetic tradition, nonetheless concede that negative styles of thinking might mediate between proximate stressors and more remote experiences. All three schools—psychoanalytic, behavioral, and cognitive—emphasize psychological constructs in explaining the origin of mood disorders. The biological models, on the other hand, are concerned with defining the somatic mechanisms that underlie or predispose to morbid affective experiences. The schism between psychological and biological conceptualizations is an instance of the mind-body dichotomy that has characterized the Western intellectual tradition since Descartes. It must not be forgotten that psychological and somatic approaches represent merely convenient investigational strategies that attempt to bypass the methodological gulf between neural and mental structures. The ultimate aim is to understand how mood disorders develop within the psychoneural framework of a given person.

AGGRESSION - TURNED - INWARD MODEL Sigmund Freud was initially interested in a psychoneural project for all mental phenomena. Limitations of the brain sciences of the day led him to adopt instead a model that relied on a concept of mental function borrowed from physics. The notion that depressed affect is derived from retroflexion of aggressive impulses directed against an ambivalently loved internalized object was actually formulated by his Berlin disciple, Karl Abraham, and later elaborated by Freud. Abraham and Freud hypothesized that turned-in anger was intended as punishment for the love object that had thwarted the depressed patient's need for dependency and love. Because, in an attempt to prevent the traumatic loss, the object had already been internalized, the patient now became the target of his or her own thanatotic impulses. A central element in those psychic operations was the depressed patient's ambivalence toward the object, which was perceived as a frustrating parent. Aggression directed at a loved object (parent) was therefore attended by considerable guilt. In the extreme such ambivalence, guilt, and retroflexed anger could lead to suicidal behavior.

According to that model, depression was an epiphenomenon of the transduction of thanatotic energy, a reaction that took place in the closed hydraulic space of the mind. In Freud's earlier writings anxiety had similarly been viewed as derived from the transformation of dammed-up sexual libido. Although Freud envisioned that neuroanatomical localization of psychoanalytic constructs would one day be realized, the hydraulic mind is a metaphor that does not refer to actual physiochemical space in the brain.

The conceptualization of emotional behavior as an arena of incompatible forces confined to a psyche that is relatively impervious to current influences outside the organism is the major liability of the aggression-turned-inward model and perhaps of orthodox psychoanalysis itself. Although the sexual energy transduction hypothesis of anxiety has been discarded in modern psychoanalytic thought, in modified version the aggression-turned-inward model continues to be used in clinical conceptualization today. The lingering popularity of the model may be due in part to its compatibility with the clinical observation that many depressed patients suffer from lack of assertion and outwardly directed aggressiveness. Yet a substantial number of hostile depressed patients are also encountered in clinical practice, and clinical improvement typically leads to a decrease rather than increase in hostility. Those observations shed doubt on the aggression-turned-inward mechanism as a universal explanation for depressive behavior. Finally, there is little evidence to support the contention that the outward expression of anger is of therapeutic value in clinical depression.

Outwardly directed hostility in depression is not a new clinical observation—the Greco-Roman physicians cited earlier noted as much—and can be considered a common manifestation rather than cause of depressive disorder, especially when the disorder is attended by mixed bipolar features. The hostility of the depressed patient can also be understood as an exaggerated reaction to frustrating love objects, as secondary to self-referential attributions, or simply as nonspecific irritability of an ego in affective turmoil. Such commonsense explanations that do not invoke unobservable hydraulic transmutations have greater appeal from heuristic and clinical perspectives.

OBJECT LOSS AND DEPRESSION Object loss refers to traumatic separation from significant objects of attachment. Ego-psychological reformulations of the Abraham-Freud conceptualization of depression have paid greater attention to the impact of such losses on the ego, de-emphasizing the id-libid-

TABLE 16.1-2
Contemporary Major Models of Depression

Proponents (Year)	Model	Mechanism	Scientific and Clinical Implications
Karl Abraham (1911)	Aggression-turned-inward	Transduction of aggressive instinct into depressive affect	Hydraulic mind closed to external influences Nontestable
Sigmund Freud (1917) John Bowlby (1960)	Object loss	Disruption of an attachment bond	Ego-psychological Open system Testable
Edward Bibring (1953)	Self-esteem	Helplessness in attaining goals of ego ideal	Ego-psychological Open system Social and cultural ramifications
Aaron Beck (1967)	Cognitive	Negative cognitive schemata as intermediary between remote and proximate causes	Ego-psychological Open system Testable Predicts phenomenology Suggests treatment
Martin Seligman (1975)	Learned helplessness	The belief that one's responses will not bring relief from undesirable events	Testable Predicts phenomenology Predicts treatment
Peter Lewinsohn (1974)	Reinforcement	Low rate of reinforcement, or reinforcement presented noncontingently; social deficits might preclude responding to potentially rewarding events	Testable Predicts phenomenology Predicts treatment
Joseph Schildkraut (1965) William Bunney and John Davis (1965) Alec Coppen (1968) I. P. Lapin and G. F. Oxenkrug (1969) David Janowsky et al (1972) Arthur Prange et al (1974) Larry Siever and Kenneth Davis (1985)	Biogenic amine (neurochemical)	Impairment or dysregulation of aminergic transmission	Testable Reductionistic Explains phenomenology and opposite episodes Suggests treatment
Alec Coppen and D. M. Shaw (1963) Peter Whybrow and Joseph Mendels (1968) Robert Post (1990)	Neurophysiological	Electrophysiological disturbances leading to neuronal hyperexcitability and kindling	Testable Reductionistic Explains phenomenology and recurrence Suggests treatment
Hagop Akiskal and William McKinney (1973) Peter Whybrow and Anselm Parlatore (1973) Frederick Goodwin and Kay Jamison (1990)	Final common pathway	Stress-diathesis interaction converging on midbrain mechanisms of reward and biological rhythms	Testable Integrative, psychobiological Pluralistic Explains phenomenology Suggests treatment

The dates provided for the models refer to the original paper or work in which they first appeared. In some instances, the bibliography at the end of the section provides references reflecting more updated thinking by those authors.

Table adapted from H Akiskal, W McKinney: Overview of recent research in depression: Integration of 10 conceptual models into a comprehensive clinical frame. Arch Gen Psychiatry *32*: 285, 1975.

inal and related hydraulic aspects. It is often noted that the depressant impact of separation events resides in their symbolic meaning for a person rather than in any arbitrary objective weight that the event may have for clinical raters. However, love loss, bereavement, and other exits from the social scene, as defined by the London psychiatrist Eugene Paykel, are presently the concepts most commonly used in practice and research.

Although love melancholy had been described since antiquity, it was in Freud's 1917 paper on mourning and melancholia that grief and melancholia were systematically compared for the first time. According to current data, the transition from grief to pathological depression occurs in no more than 2 to 5 percent of adults and 10 to 15 percent of children. Those figures suggest that such transition occurs largely in persons predisposed to mood disorders.

The work of John Bowlby of the Tavistock Clinic, London, is a comprehensive clinical investigation of the attachment that the child establishes with the mother or mother substitutes during development; that bond is considered the prototype for all subsequent bonds with other objects. Like many psychoanalytic explanations of adult symptom-formation, the object loss model is formulated as a two-step hypothesis, consisting of early breaks in affectional bonds, which provide the behavioral predisposition to depression, and adult losses, which are said to revive the traumatic childhood loss, thereby precipitating depressive episodes. However, the role of proximate separations in provoking depressive reactions rests on more solid clinical evidenee than the hypothesized sensitization resulting from developmental object loss. That realization has led Bowlby to regard childhood sensitization resulting from early deprivation as a generic characterological vulnerability to a host of adult psychopathological conditions.

Compared with aggression turned inward, object loss is more directly relevant to clinical depression; yet it is still pertinent to question whether it is an etiological factor. Studies at the Wis-

consin Primate Center have indicated that optimal homeostasis with the environment is most readily achieved when the individual is securely attached to significant others, and the dissolution of such ties appears relevant to the emergence of a broad range of psychopathological disturbances rather than depression per se. A related methodological question is whether object loss operates independently of other etiological factors. For instance, a history of early breaks in attachment may reflect the fact that one or both of the patient's parents had mood disorder, with resultant separation, divorce, suicide, and so forth.

On balance, the ego-psychological object loss model is conceptually superior to its id-psychological counterpart. In postulating an open system of exchange between a person and the environment, the model permits consideration of etiological factors other than separation—such as heredity, character structure, and adequacy of social support—all of which might modulate the depressant impact of adult separation events. Conceptualizing the origin of depression along those lines is in the mainstream of current ideas of adaptation, homeostasis, and disease. An important treatment implication is the value of social support in preventing relapse and mitigating chronicity of depression. That is indeed an ingredient in the interpersonal psychotherapy of depression, which can be conceptualized as a form of brief, focused, and practical psychodynamic therapy.

DEPRESSION AS LOSS OF SELF-ESTEEM Reformulation of the dynamics of depression in terms of the ego suffering a collapse of self-esteem represents a further conceptual break with the original id-psychological formulation: Depression is said to originate from the ego's inability to give up unattainable goals and ideals. The model further posits that the narcissistic injury that crushes the depressed patient's self-esteem is imposed by the internalized values of the ego rather than the hydraulic pressure of retroflected thanatotic energy deriving from the id. Because the construct of the ego is rooted in social and cultural reality, loss of self-esteem may result from symbolic losses involving power, status, roles, identity, values, and purpose for existence. Thus, the existential and sociocultural implications of depression conceived as a derivative ego state provide the clinician with a far more flexible and pragmatic tool for understanding depressed persons than the archaic hydraulic metaphors related to libidinal vicissitudes. That model represents one of the first attempts to formulate depression in terms that subsequent psychological theory and research could operationalize in more testable form.

Self-esteem is part of the habitual core of the individual and as such is integral to the personality structure. Indeed, low self-esteem conceived as a trait is a major defining attribute of the depressive (melancholic) personality. While it is understandable how such individuals can easily sink into melancholia in the face of environmental adversity, it is not obvious why persons with apparently high self-esteem, such as those with hypomanic and narcissistic personalities, also succumb to melancholy with relative ease. To explain such cases, one must invoke an underlying instability in the system of self-esteem that renders it vulnerable to depression. The opposite is also known to occur; that is, manic episodes may develop from a baseline of low self-esteem, as sometimes occurs in patients with dysthymic disorder.

The foregoing considerations suggest that the vicissitudes of self-esteem deemed central to the model of depression as loss of self-esteem are manifestations of a more fundamental mood dysregulation. In classical psychoanalysis it is conceded that such dysregulation is of constitutional origin. In general, attempts by psychoanalytic writers to account for bipolar oscillations have not progressed beyond metapsychological jargon, with the possible exception of denial of painful affects as a mechanism in the phenomenology of mania.

COGNITIVE MODEL The cognitive model, developed by Aaron Beck at the University of Pennsylvania, hypothesizes that thinking along negative lines (for example, thinking that one is helpless, unworthy, or useless) is the hallmark of clinical depression. In effect, depression is redefined in terms of a cognitive triad, according to which the patient thinks of him- or herself as helpless, interprets most events in an unfavorable light vis-à-vis the self, and believes the future to be hopeless. In more recent formulations in academic psychology, those cognitions are said to be characterized by a negative attributional style that is global, internal, and stable and to exist in the form of latent mental schemata that generate biased interpretations of life events.

Because the cognitive model is based on retrospective observations of already depressed persons, it is virtually impossible to prove that causal attributions such as negative mental schemata precede and hence predispose to clinical depression; they can just as readily be regarded as clinical manifestations of depression. The importance of the cognitive model lies in the conceptual bridge it provides between ego-psychological and behavioral models of depression. It has also led to a new system of psychotherapy that attempts to alter the negative attributional style, to alleviate the depressive state, and, ultimately, to fortify the patient against future lapses into negative thinking, despair, and depression.

The cognitive model therefore has the cardinal virtue of focusing on key reversible clinical dimensions of depressive illness, such as helplessness, hopelessness, and suicidal ideation, while providing a testable and practical psychotherapeutic approach. That approach, however, is less likely to succeed in patients with the full-blown melancholic manifestations of a depressive disorder. It is doubtful that negative cognitions alone could account for the profound disturbances in sleep, appetite, and autonomic and psychomotor functions encountered in melancholic depressions. Further, to conceptualize a multifaceted malady such as depression largely or solely as a function of distorted cognitive processes is reminiscent of pre-Esquirolian notions that emphasized impaired reasoning in the development of depression.

LEARNED HELPLESSNESS The learned helplessness model is in some ways an experimental analog of the cognitive model. The model proposes that the depressive posture is learned from past situations in which the person was unsuccessful in initiating action to terminate undesirable contingencies. The model is based on experiments in dogs that were prevented from taking adaptive action to avoid unpleasant electrical shock and subsequently showed no motivation to escape such aversive stimuli, even when escape avenues were readily available. Armed with evidence from many such experiments, the University of Pennsylvania psychologist Martin Seligman postulated a trait of learned helplessness—a belief that it is futile to initiate personal action to reverse aversive circumstances—that is formed from the cumulation of past episodes of uncontrollable helplessness.

The learned helplessness paradigm is a general one and refers to a broader mental disposition than depression. Thus, it is potentially useful in understanding such diverse conditions as social powerlessness, defeat in sporting events, and posttrau-

matic stress disorder. In addition, past events might shape a characterological cluster, consisting of passivity, lack of hostility, and self-blame, relevant to certain depressive phenomena. The low hostility observed in some patients during clinical depression could, for instance, be ascribed to the operation of such factors. Learned helplessness could thereby provide plausible links between aspects of personal biography and clinical phenomenology in depressive disorders. Therapeutic predictions for alleviating depression and related psychopathological states capitalize on new cognitive strategies geared to modifying expectations of uncontrollability and the negative attributional style. That is an illustration on how insights gained from experimental paradigms can be fruitfully combined to address clinical disorders.

Nonetheless, the clinician should be wary of unwarranted clinical extrapolations. For instance, some clinicians have argued that the depressed patient's passivity is manipulative, serving to obtain interpersonal rewards. It has also been claimed that such factors have a formative influence on the development of the depressive character. That interpretation appears more relevant to selected aspects of depression than to the totality of the disorder. Depressive behavior and verbalizations clearly have a powerful interpersonal impact, but to speculate that depression represents merely a masochistic life-style developed for the purpose of securing interpersonal advantages represents a circular argument that is mechanistic and could be viewed as disrespectful of the clinical agony of patients with mood disorders. Finally, although most formulations focusing on helplessness have emphasized acquisition through learning, recent experimental research in animals tends to implicate genetic factors in the vulnerability to learning to behave helplessly.

REINFORCEMENT AND DEPRESSION Other behavioral investigators, notably Peter Lewinsohn, have developed clinical formulations of depression that hinge on certain deficits in reinforcement mechanisms. According to the reinforcement model, depressive behavior is associated with lack of appropriate rewards and, more specifically, with the receipt of noncontingent rewards. The model identifies several contributory mechanisms. Some environments may consistently deprive persons of rewarding opportunities, thereby placing them in a chronic state of boredom, pleasurelessness, and, ultimately, despair. That reasoning, however, may offer more insight into social misery than clinical depression. A more plausible postulated mechanism is the provision of rewards that are not in response to the recipient's actions; in other words, the gratis provision of what a person considers undeserved rewards may lead to lowering of self-esteem. Predisposition to depression is formulated in terms of deficient social skills, which are hypothesized to decrease a person's chances of responding to potentially rewarding contingencies in any environment. Indeed, recent research on the relation between personality and mood disorder suggests that such deficits might contribute to certain nonbipolar depressions. Therefore, psychotherapeutic approaches designed to enlarge a patient's repertoire of social skills may prove valuable in preventing depressive episodes.

The concepts of depression that have been derived from behavioral methodology and developed in the past three decades are scientifically articulate and therefore testable approaches to the clinical phenomena of depression. Yet in the behavioral literature the distinction between depression on self-report inventories and clinical depression is sometimes overlooked. Further, the behavioral model does not address the distinct possibility that reinforcement deficits may simply represent the psychomotor inertia of depressive illness. Nevertheless, by focusing on reward mechanisms, the behavioral model provides a conceptual bridge between purely psychological and emerging biological conceptualizations of depression.

BIOGENIC AMINE IMBALANCE

Chemistry of the emotional brain The formulation of sophisticated biological explanations of mood disorders had to await the development of neurobiological techniques that could probe parts of the brain involved in emotions. Although the complex physiology of the limbic-diencephalic centers of emotional behavior is generally inaccessible to direct observation in humans, much has been learned from animal work. The limbic cortex is linked with both the neocortex, which subserves higher symbolic functions, and the midbrain and lower brain centers, which are involved in autonomic control, hormonal production, and sleep and wakefulness. Norepinephrine-containing neurons are involved in many of the functions that are profoundly disturbed in melancholia, including mood, arousal, appetite, reward, and drives. Other biogenic amine neurotransmitters that mediate such functions are the catecholamine dopamine, especially important for psychomotor activity, and the indoleamine serotonin, involved in mood and sleep and inhibitory control. Cholinergic neurons, secreting acetylcholine at their dendritic terminals, are generally antagonistic in function to catecholaminergic neurons. Although the opioid system might, on experimental and theoretical grounds, also serve as one of the neurochemical substrates for mood regulation, in the author's opinion no cogent model of mood disorders involving that system has appeared to date.

Biogenic amine hypotheses Joseph Schildkraut at Harvard University and William Bunney and John Davis at NIMH published the first reports formally hypothesizing a connection between depletion or imbalance of biogenic amines, specifically norepinephrine, and clinical depression. The serotonin counterpart of the model was emphasized in the models proposed by Alec Coppen in England and I.P. Lapin and G.F. Oxenkrug in Russia. Both catecholamine and indoleamine hypotheses were essentially based on two sets of pharmacological observations. First, reserpine, a medication that decreases blood pressure by depleting biogenic amine stores, was known to precipitate clinical depression in some patients. Second, antidepressant medications, which alleviate clinical depression, were found to raise the functional capacity of the biogenic amines in the brain. That style of thinking is known as the pharmacological bridge, extrapolating from evidence on mechanism of drug action to the neurotransmitter pathologies presumed to underlie a given psychiatric disorder. Such pharmacological strategies have been of heuristic value in developing research methods for the investigation of mood disorders and schizophrenia. Indeed, the research methodology developed by the relatively few investigators working in the area in the past three decades is among the most elegant in the history of psychiatry.

Different variations of the biogenic amine model give somewhat different importance to the relative weight of the biogenic amines norepinephrine and serotonin in the development of pathological mood states. Arthur Prange and colleagues at the University of North Carolina formulated a permissive biogenic amine hypothesis according to which serotonin deficits permit the expression of catecholamine-mediated depressive or manic states. That hypothesis was supported by subsequent animal research showing that an intact serotonin system is necessary

for the optimal functioning of noradrenergic neurons. In a recent study, the omission of tryptophan from the diet of antidepressant-responsive depressed patients annulled the efficacy of the antidepressant. Although that finding is intriguing, the precursor-loading strategy to increase the brain stores of serotonin (for example, with L-tryptophan) has not been unequivocally successful in addressing clinical depression. Dietary loading with catecholamine precursors has fared even worse than serotonin precursor loading in the treatment of depression.

The cholinergic-noradrenergic imbalance hypothesis as proposed by David Janowsky and colleagues represents yet another attempt to elucidate the roles of biogenic amines. More recent formulations by Larry Siever and Kenneth Davis at the Mount Sinai Hospital in New York have hypothesized noradrenergic dysregulation as an alternative neurochemical mechanism for depressive disorders. The model envisions oscillation from one output mode to the other at different phases of depressive illness. In a provocative extrapolation from that model, bipolar depression would emerge as being of low noradrenergic output, but many instances of major depressive disorder, like some anxiety disorders, could be biochemically conceptualized as high-output conditions.

Despite three decades of extensive research and indirect evidence, however, it has not been proved that a deficiency or excess of biogenic amines in specific brain structures is necessary or sufficient for the occurrence of mood disorders. The role of dopamine, though less extensively studied than that of norepinephrine, deserves greater recognition: It might have relevance to atypical and bipolar depression as well as mania. The putative permissive role of serotonin appears more relevant to aggressive suicide attempts than to depression per se. It is also of theoretical and clinical interest that serotonergic dysfunction might subserve other conditions characterized by lack of inhibitory control, among them obsessive-compulsive and panic phenomena, bulimia nervosa, certain forms of insomnia, alcoholism, and a host of impulse-ridden personality disorders. Such considerations have led the Dutch psychiatrist Herman van Praag and his colleagues to postulate a dimensional neurochemical disturbance generic to a large group of disorders within the traditional nosology. That hypothesis might be variously regarded as a challenge to psychiatric nosology or as a statement of the need to supplement clinical classification with biochemical parameters.

The biogenic amine models provide meaningful links with the clinical phenomena of, and the pharmacological treatments currently employed in, mood disorders. Although the predisposition to mood disorder is not specified in those models, it is implied that the biochemical faults are genetically determined.

Neuroendocrine links Inadequate or excessive mobilization of neurotransmitters such as noradrenaline in the face of continued or repeated stress, as reflected in pathological modification of noradrenergic receptor function, could represent a neurochemical final common pathway of homeostatic failure. Such mechanisms could also provide links with psychoendocrine dysfunction; the hypothesized neurotransmitter deficits may underlie the disinhibition of the hypothalamic-pituitary-adrenal axis, characterized by steroidal overproduction, the most widely studied endocrine disturbance in depressive illness. When challenged with dexamethasone, the altered axis has been found resistant to suppression, thereby offering Bernard Carroll and colleagues at the University of Michigan the possibility of developing the dexamethasone suppression test (DST) for melancholia (the test is currently of uncertain specificity for melancholia). That line of research has culminated in the demonstration by Charles Nemeroff and other investigators of increased concentrations of corticotropin-releasing factor (CRF) in the cerebrospinal fluid of patients with major depressive disorder. CRF also appears relevant to the pathophysiology of anxiety disorders, such as panic disorder.

Another neuroendocrine index of noradrenergic dysregulation—blunted growth hormone response to the α_2-adrenergic receptor agonist clonidine—likewise points to limbic-diencephalic disturbance. However, studies performed in the United States suggest that it is positive in both endogenous depression and severe anxiety disorder (panic disorder). Thyroid-stimulating hormone (TSH) blunting upon thyrotropin (TRH) stimulation, another common neuroendocrine disturbance in depression, is also of limited specificity (it is often positive in alcoholism).

What is remarkable, however, is that the DST, clonidine, and TRH challenge data in aggregate identify the majority of persons with clinical depression. The more relevant point is that such evidence of midbrain disturbance argues for considering clinical depression a legitimate illness. Finally, the data tend to argue for shared mechanisms between certain mood and anxiety disorders.

Stress, biogenic amines, and depression The concept of a pharmacological bridge implies two-way traffic. The hypothesized chemical aberrations may be primary or biologically induced. Provision should also be made, however, for the likelihood that psychological events, which serve as precipitants of clinical depression, might induce or initiate neurochemical imbalance in vulnerable subjects. That suggestion is supported by studies in animals, where separation and inescapable frustration are known to effect profound alterations in the turnover of biogenic amines and in postsynaptic receptor sensitivity. It is conceivable that, in genetically predisposed persons, environmental stressors might more easily lead to perturbations of limbic-diencephalic neurotransmitter balance. Finally, it is plausible that in vulnerable individuals, especially during the formative years of childhood, the psychological mechanisms discussed earlier might more easily perturb midbrain neurochemistry.

NEUROPHYSIOLOGICAL APPROACHES

Electrolyte metabolism and neuronal hyperexcitability

Abnormalities in neuronal electrolyte balance (an excess of residual sodium, defined by radioisotope techniques) and hypothesized secondary neurophysiological disturbances were the focus of investigations by Coppen and colleagues in the early 1960s. The existing data appear compatible with the hypothesized movement of excess sodium into the neuron during an episode of mood disorder and redistribution toward the preillness electrolyte balance across the neuronal membrane during recovery; intraneuronal leakage of sodium is postulated in both depressive and manic disorders but deemed more extreme in the latter. Because the harmonious activity of the neuronal cell—and, by implication, that of a group of neurons—depends on the electrical gradient maintained across its membrane by the differential distribution of sodium, abnormalities in sodium concentrations and transport are hypothetically relevant to the production of an unstable state of neurophysiological hyperexcitability.

The view that mania represents a more extreme electrophysiological dysfunction in the same direction as depression violates the commonsense notion of symptomatological opposition between the two kinds of disorder, yet it may in part account for the existence of mixed states in which symptoms of depression and mania coexist. That many depressed patients with a

bipolar substrate respond to lithium salts—a provocative finding first documented by the NIMH team led by Frederick Goodwin—further supports the concept of a neurophysiological common denominator to mania and depression.

Rhythmopathy and depression Recent neurophysiological formulations by Thomas Wehr and Norman Rosenthal, working at NIMH, have focused on abnormalities in the circadian regulation of temperature, activity, and sleep cycles, thereby paving the way for new theoretical constructs and therapeutic possibilities. It has been found that depressed patients are phase-advanced in many of their biological rhythms, including the latency to first rapid eye movement (REM) in sleep. Shortening of REM latency, which has been extensively studied by David Kupfer and colleagues at the University of Pittsburgh, has been proposed as another biological test for depressive disorder. Finally, it has been hypothesized that sleep deprivation (originally developed by European investigators) and exposure to bright white light (demonstrated by NIMH research) might correct phase disturbances and thereby terminate depressive episodes, especially in patients with periodic and seasonal illness. Although the specificity and efficacy of those neurophysiological indices and manipulations for mood disorders require more extensive research, cumulatively they point to midbrain dysregulation as the likely common neurophysiological substrate of depressive disorders.

The foregoing considerations further suggest that the ancient Greeks, who ascribed melancholia to malignant geophysical influences, did not indulge in mere poetic metaphor. It is also striking that the ancients had observed the disturbed circadian patterns and advocated their readjustment to restore euthymia.

Affective dysregulation as the fundamental pathology The ultimate challenge for research in mood disorders is to characterize the basic molecular mechanisms that underlie the neurophysiological rhythmopathies, which in turn might account for the recurrent nature of the affective pathology as envisioned by Kraepelin. This means that in the most typical recurrent forms of the disorders, the constitutional foundations—manifested as cyclothymic and dysthymic temperaments—are so unstable that the illness may run its entire course more or less autonomously, with the environment largely serving the role of turning on and off the more florid phases (episodes). The Parisian psychiatrist Jean Delay also emphasized affective dysregulation as the fundamental pathology in the spectrum of mood disorders. Robert Post, at NIMH, has hypothesized that the electrophysiological substrates could be kindled, such that an oligoepisodic disorder, initially triggered by environmental stressors, could assume an autonomous and polyepisodic course. The monograph on manic-depressive illness by Goodwin and Kay Jamison presents eloquent arguments for a fundamental cyclical thymopathy, based on current psychobiological understanding.

CONCEPTUAL INTEGRATION

TOWARD PATHOPHYSIOLOGICAL UNDERSTANDING

Modern psychobiology attempts to link experience and behavior to the central nervous system. To build sturdy conceptual bridges between the psychological and biological approaches to mood disorders, sophisticated strategies are needed that go beyond the Cartesian notion of limited mind-body interactions through the pineal gland and the more pedestrian generalizations of the Meyerian school.

In collaboration with Peter Whybrow at the University of Pennsylvania, William McKinney and the author have further developed the conceptual framework that considers the syndromes of melancholia and mania as the final common pathway of various psychological and biological processes. The overarching hypothesis is that psychological and biological etiological factors converge in reversible deficits in the diencephalic substrates of pleasure and reward. Those areas of the brain subserve the functions that are disturbed in melancholia and mania. The integrative model links the central chemistry and physiology of reward mechanisms with the object loss and behavioral models of depression, both of which give singular importance to the depressant role of loss of rewarding interpersonal bonds; an essential element of the model is the circadian disturbances observed since ancient times in both depressive and manic syndromes. Both syndromes then are conceptualized as the clinical manifestations of a disordered limbic system with its subcortical and prefrontal extensions. Multiple factors converge in producing dysregulation in the system and are described below.

Predisposing heredity Current evidence indicates that genetic factors play a significant role in the causation of bipolar and recurrent major depressive disorders. Genetic heterogeneity is likely, and may involve single-gene-dominant inheritance with variable penetrance or polygenic inheritance. Although it is not known exactly what is inherited, recent research by Kenneth Kendler and associates suggests that heritability involves a broad spectrum of disorders, including milder depressive episodes.

Developmental predisposition As parents with mood disorders are often in conflict, which may lead to separation, divorce, and suicide, it can be said that heredity often determines the type of environment into which the child predisposed to mood disorder is born. Developmental object loss, although not causing mood disorder, might modify the expression of the illness, possibly by leading to earlier onset, more severe episodes, and an increased likelihood of personality disorder and suicide attempts.

Temperament Since ancient times, persons prone to mania and melancholia have been described as possessing certain temperamental attributes, representing variations on the theme of what today is subsumed under cyclothymia and dysthymia. The fact that many monozygotic twins discordant for mood disorders studied by Aksel Bertelsen's Danish research team exhibited affective instability along such temperamental lines strongly suggests that such attributes represent genetically determined traits. That research and research conducted by Kendler and associates suggest that many of the temperamental attributes might be transmitted as part of the overall genetic liability to mood disorders. The author's research has identified those temperaments in the prepubertal offspring of parents with bipolar (manic-depressive) disorders, suggesting that they precede by years to decades the onset of major mood disorder episodes. Those temperaments in turn generate much interpersonal friction, emotional arousal, and sleep loss, and thereby might give rise to many of the life stressors that precipitate episodes of mood disorders. The use of stimulant drugs—either to self-treat lethargy or enhance hypomanic episodes—can also precipitate such episodes.

Life events Most individuals do not develop clinical depression when exposed to environmental adversity. Such adversity seems to play a pathogenic role in those with an affective diathesis. Thus, current data suggest that social stressors in the onset of depression are more relevant to the early course of the illness. The evidence linking such events to mania is less robust. At any rate, socially stressful events often appear to be triggered by the temperamental instability that precedes clinical episodes. Interpersonal losses are common events in the lives of individuals with intense temperaments. Indeed, a recent study by Peter McGuffin and associates at the Institute of Psychiatry, London, raised the possibility that one mechanism by which heredity produces depression is by creating environmental adversities in the lives of individuals predisposed to this illness. Whatever the origin of environmental adversity, it is common clinical experience that loss represents an important—perhaps even central—theme in clinical depression. Variables that seem to modulate the impact of adult losses include concurrent life events, resultant changes in life-style, lack of interper-

sonal support, deficient social skills, and the symbolic meaning of the loss.

Biological stressors Many physical diseases and pharmacological agents are known to precede the onset of both depressive and manic episodes. Like psychosocial stressors, however, they do not generally seem to cause de novo episodes but mobilize them in those persons with a personal and family history of mood disorders.

Sex Clinical and epidemiological studies concur in suggesting that women are at higher risk for mood disorders, with the risk highest for the milder depressive states. Although it is customary to ascribe the increased risk to social and interpersonal variables, biological factors appear equally relevant. Women have higher levels of brain monamine oxidase (the enzyme that breaks down monamine transmitters), have more precarious thyroid status (often associated with chronic and rapid-cycling mood episodes), experience postpartum precipitation, experience premenstrual accentuation of dysphoric mood, and are vulnerable to the depressant effect of steroidal contraceptives. Recent data reported by Giulio Perugi and associates at the University of Pisa, Italy, have raised the hypothesis that female sex might also favor the greater expression of dysthymic attributes, whereas hypomanic traits appear favored by male sex. Those considerations tend to parallel, respectively, the ruminative and active cognitive response styles reported by Stanford's Susan Nolen-Hoeksema to distinguish the sexes. What specific sex-related biographical factors might interact with sex-related biological factors to produce such trait differences is presently unknown.

The model presented here (Figure 16.1-3) goes beyond the general provisions of the unified approach developed two decades earlier. It is submitted that, at least in the highly recurrent forms of the malady, affective temperaments represent the intermediary stage between remote (for example, hereditary) and proximate (for example, stressful) factors, and that limbic-diencephalic dysfunction is best characterized as the biological concomitant of the clinical manifestations of the affective syndromes. Like the temperamental dysregulations, those biological disturbances represent a stage in the pathogenetic chain: They emerge as temperamental instabilities that react to, provoke, or invite life events, substance use, and rhythmopathies, which in turn usher in the behavioral and subjective manifestations of the illness.

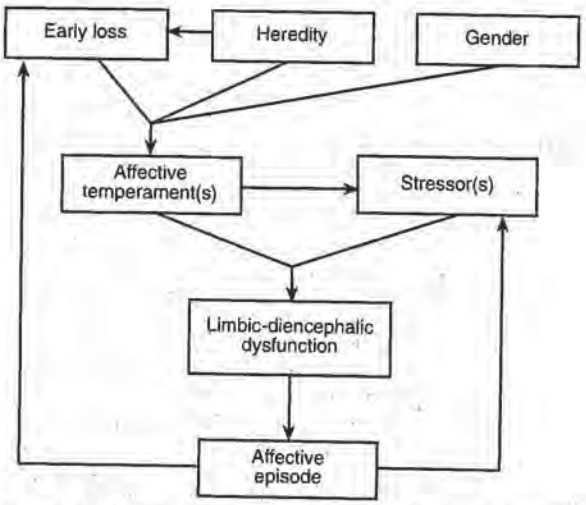

FIGURE 16.1-3 *An integrative pathogenetic model of mood disorders.*

IMPLICATIONS FOR TREATMENT AND PREVENTION

The foregoing integrative model envisions the joint use of somatic-pharmacological and psychosocial interventions. Although the milder forms of mood disorders can be managed with psychotherapy, somatic treatments are usually required for reversing the biological disturbances in melancholia before the patient can respond to interpersonal feedback. Depressive disorders with psychotic features often necessitate more definitive somatic interventions such as electroconvulsive therapy. Continued psychopharmacological treatment is also effective in decreasing rates of relapse and future recurrence.

Psychosocial therapy by skilled therapists can provide support, combat demoralization, change maladaptive self-attributions, and improve conjugal and vocational functioning. Whether such therapy can also modify personality traits to fortify the patient against new episodes is a future research challenge. In the author's view, it may prove more profitable to attempt to help patients explore professional and object choices that match their temperamental proclivities and assets and that in turn might provide them greater harmony and adaptation in life. Although much needs to be learned about the indications for medication and psychotherapy in different subtypes of mood disorders, research to date not only does not indicate a negative interaction between the two forms of treatment but in some instances suggests additive and even synergistic interaction.

The challenge for psychiatric research in the decade ahead is to elucidate the basic mechanisms whereby the predisposing, precipitating, and mediating variables reviewed here, and others yet to be identified, interact to produce the final common path of decompensation in melancholia. Because of the heterogeneity of depressive conditions presenting as a psychobiological final common syndrome, and because antidepressant agents, irrespective of specificity to one or another biogenic amine, are about equally effective in two thirds of those with depressive disorder with melancholic features, the antidepressant agents, effective as they are, may be acting not on the primary lesions of the depressive disorders but on a neurochemical substrate distal to the underlying biological faults. The choice of antidepressants is still very much guided by the side effect profile least objectionable to a given patient's constitution, physical condition, and life-style.

Current evidence suggests that in depressed patients with bipolar disorder antidepressants might provoke mixed episodes, hypomanic episodes, or both and, possibly, increased cycling in the subsequent course of the disorder. The value of lithium in such cases does suggest some biochemical specificity. The kindling-sensitization model further suggests the utility of anticonvulsant medication on escalation of the disorder and represents another example of pathophysiology-based intervention. Interventions geared to disturbed rhythms of the disorder represent yet another example. Thus, mood clinics should educate patients and their significant others on how to dampen stimulation so that it is kept at an optimal level for depressed patients with cyclothymic disorder. All offending drugs (for example, cocaine, caffeine) should be eliminated and circadian disruptions and sleep loss minimized. The greater challenge is how to curb the tempestuous romantic liaisons or ill-fated financial ventures that periodically jolt the lives of patients with cyclothymic disorder. Psychoeducation and psychotherapy have the task of ameliorating the resulting social problems. Assuring compliance to a lithium regimen—which in many would have attenuated episodes and prevented such sequelae—is not easily achieved. Research on both compliance-enhancing techniques and the physiochemical mechanisms of lithium is needed before

the drug can be used efficiently in the large number of patients who might benefit from it.

It is tempting to suggest that biogenic amines, the humors of modern psychobiology, play the same heuristic role as the ancient humors did for many centuries. The black humor, appropriately evoked in the construct of melancholia in DSM-IV, may not have the same claim for etiological relevance to depressive disorders as biogenic amines but at least has a classical heritage. In any discipline, scientific truth is a function of its technology, but understanding the phenomena under consideration is a matter of philosophical temperament that seeks integration and the hope for a unified vision. Research into the causes and treatment of mood disorders has generated an abundance of recent data suitable for integration into theory and practice, and conceptualizing the origin and treatment of mood disorders can no longer be justified on the ground of ideological preference alone.

SUGGESTED CROSS-REFERENCES

The other sections of Chapter 16 cover the various aspects of mood disorders in detail. Epidemiology is the subject of Section 16.2; biochemical aspects are the focus of 16.3; Section 16.4 is a discussion of genetic aspects; psychodynamic etiology is the subject of Section 16.5. Clinical features are covered in Section 16.6, somatic treatment in Section 16.7, and a discussion of psychosocial treatments concludes the chapter in Section 16.8.

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16.2 MOOD DISORDERS: EPIDEMIOLOGY

DAN BLAZER II, M.D., Ph.D.

INTRODUCTION

The epidemiological study of mood disorders complements clinical investigation of those disorders by completing the clin-

ical picture in breadth and through time. The clinician's experience with a chronic syndrome, such as depression, is limited to the hospital and the outpatient setting. The epidemiologist broadens the study to community populations and studies the natural history of those syndromes through time. The tasks of epidemiology have been applied to the mood disorders by many investigators in recent years. Those tasks include: identification of cases (for example, What is a case of major depressive disorder?), distribution of cases (for example, Do blacks experience more depressive disorders than nonblacks?), historical trends (for example, Is major depressive disorder becoming more prevalent in the population as one nears the end of the 20 century?), identification of causes (for example, Does low socioeconomic status predispose to the onset of major depressive disorder?), prognosis (for example, What is the likelihood of disability from a major depressive episode within the first year after a case is diagnosed?), and need demand, supply, and use of psychiatric services (for example, What percentage of persons with mood disorders in the community receive care from a mental health specialist?).

Most of the data presented here derive from studies of depressive symptoms and the diagnosis of major depressive disorder. Bipolar disorders will receive less attention than they do in clinical studies because the community-based epidemiological data are sparse. The lifetime prevalence of some mood disorders, including dysthymic disorder and cyclothymic disorder, appears in Table 16.2-1.

CASE IDENTIFICATION

Clinicians who treat patients experiencing mood disorders must distinguish normal variations in mood from the mood disorders. The diagnostic criteria for the specific mood disorders in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and its predecessors are not always easily applied in epidemiological studies. Some of the diagnostic categories, such as adjustment disorder with depressed mood, cannot be operationalized in standardized interviews because the criteria require a subjective clinical judgment (for example, the mood disturbance must be related to a specific stressor). Other diagnoses are too inclusive when applied to community samples, such as major depressive disorder. Cases identified using current diagnostic criteria are therefore a heterogeneous mix that has little clinical relevance beyond symptom severity. In other words, the borderline between clinical depression and normal fluctuation in mood is fuzzy. Even the presence or absence of a symptom may be disputed.

Some persons in community samples may present with depressive syndromes that do not fit the DSM diagnostic system (for example, for major depressive disorder or dysthymic disorder) but they nevertheless suffer disabling depressive symptoms. Much attention has been focused in recent years on so-called minor depressive disorder, a syndrome defined by symptoms that are less severe than major depressive disorder and of shorter duration than dysthymic disorder. Persons identified in community surveys as experiencing minor depressive disorder have been shown in prospective studies to be at greater risk for time lost at work and increased use of general health services than persons without depressive symptoms.

The process of case identification in community studies also may contribute to bias. Recall of past symptoms is only modestly accurate when compared with clinical records of previous depressive episodes. The threshold for reporting a symptom of depression may be higher in a community setting than in a clinical one because clinicians often probe for evidence of a symptom that the patient initially denies. Most of the interview instruments that are used in epidemiological surveys to identify DSM diagnoses, such as the Diagnostic Interview Survey (DIS) and the Schedule for Affective Disorders and Schizophrenia (SADS), were developed in clinical settings and were standardized using classic cases that present to psychiatric treatment settings. Depressive symptoms that are disabling to persons in the community may not always be identified by diagnostic techniques that are effective in clinical settings.

Comorbidity presents another problem to psychiatric epidemiologists who study mood disorders in community settings. More often than not, symptoms of anxiety and depression overlap. Many subjects receive concurrent diagnoses of major depressive disorder, dysthymic disorder, and generalized anxiety disorder. Most community survey subjects cannot accurately remember whether the depression or the anxiety was the first syndrome experienced. Do major depressive disorder and generalized anxiety disorder coexist, or is anxiety an epiphenomenon of major depressive disorder? That question remains unanswered.

Those problems in case identification in community surveys for psychiatric morbidity have stimulated clinical and community-based investigators to seek better case finding and case identification methods. Standardized diagnostic interviews have greatly improved the reliability of symptom identification. (For example, clinical investigators may not agree upon the utility of the diagnosis of mood disorder with seasonal pattern, also known as seasonal affective disorder, but they can test their disagreement using the same criteria for case identification and findings are therefore comparable across studies.) Explicit diagnostic criteria, such as the Research Diagnostic Criteria and its successors, provide hypotheses for testing. (For example, is bipolar I disorder, as defined by DSM-IV, more heritable than major depressive disorder? If so, then those criteria differentiate, to some extent, two different psychobiological entities.)

TABLE 16.2-1
Lifetime Prevalence of Some DSM-IV Mood Disorders

Mood Disorder	Lifetime Prevalence
Depressive disorders	
Major depressive disorder (MDD)	10-25% for women; 5-12% for men
Recurrent, with full interepisode recovery, superimposed on dysthymic disorder	Approximately 3% of persons with MDD
Recurrent, without full interepisode recovery, superimposed on dysthymic disorder (double depression)	Approximately 25% of persons with MDD
Dysthymic disorder	Approximately 6%
Bipolar disorders	
Bipolar I disorder	0.4-1.6%
Bipolar II disorder	Approximately 0.5%
Bipolar I disorder or bipolar II disorder, with rapid cycling	5-15% of persons with bipolar disorder
Cyclothymic disorder	0.4-1.0%

Data from DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, ed 4. Copyright American Psychiatric Association, Washington, 1994.

DISTRIBUTION OF CASES

The prevalence of the most common mood disorders by age and sex is presented in Figure 16.2-1. Those data are derived from the largest community-based epidemiological case finding

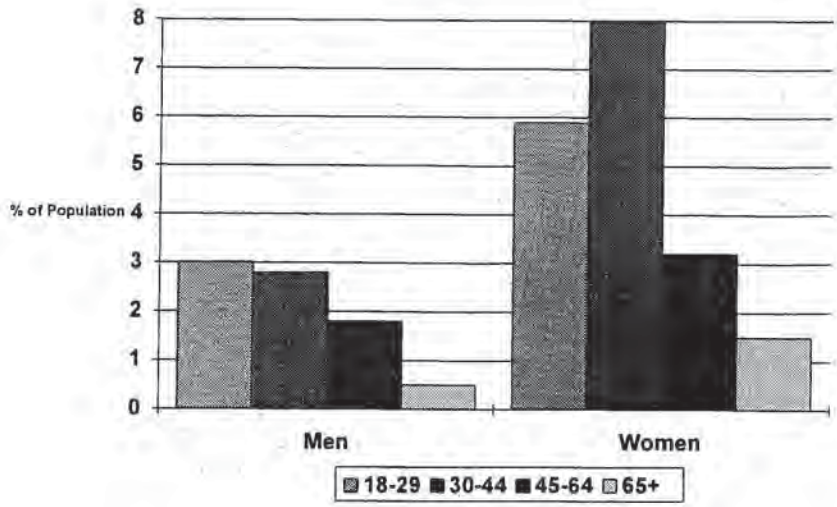


FIGURE 16.2-1 *Prevalence of the most common mood disorders by age and sex. Data derived from the Epidemiologic Catchment Area study.*

study fielded in western society—the Epidemiologic Catchment Area (ECA) Study. The Diagnostic Interview Schedule was administered to over 18,000 community and institutionalized subjects at five sites throughout the United States—New Haven, East Baltimore, St. Louis, the Piedmont of North Carolina, and Los Angeles. By virtue of the large numbers of subjects and the oversampling of subjects not accurately represented in previous studies, such as blacks, Hispanics, and the elderly, much better estimates of the actual distribution of cases were possible.

AGE AND SEX The most striking finding from the ECA study was the much higher prevalence of all the mood disorders among persons under the age of 45 compared with persons over 45 years of age. Manic episodes are about equally prevalent in men and women, whereas major depressive disorder and dysthymic disorder are more prevalent in women than in men. Rates were comparable across ECA sites, except for a lower prevalence in North Carolina. The North Carolina sample was composed of both urban and rural residents. Persons in urban areas were as likely to be diagnosed with a mood disorder in North Carolina as in urban areas at other ECA sites. In contrast, rural subjects in North Carolina had much lower rates of major depressive disorder than rural subjects at other ECA sites.

The most consistent finding across epidemiological studies of the mood disorders, confirmed by the ECA study, is the relatively higher prevalence of major depressive disorder in women than in men. The sex differences are consistent across the life cycle, but are much more prominent in young adult and middle-aged persons than in the elderly and children. Many factors have been suggested to account for this sex difference, such as endocrine physiology and genetics. Although the endocrine system of women differs significantly from that of men, there is no consistent endocrinological theory to account for the sex differences in depressive disorders. Because alcohol abuse and mood disorders are often inherited in the same family, and alcohol abuse and dependence are more prevalent in men than in women, perhaps depressive disorder and alcohol abuse and dependence are phenotypic variants of the same genotype. Little evidence, however, supports that hypothesis. Consistent findings across community-based epidemiological studies have nullified the hypothesis that depressive disorder appears to be more prevalent in women because they are more likely to seek services for depression than men. Psychosocial explanations for the higher prevalence of depressive disorders among women are currently considered the most promising. For example, the greater stress for women of maintaining multiple roles, such as homemaker, professional, wife, and mother is one possible explanation.

RACE As illustrated in Figure 16.2-2, the prevalence of the mood disorders does not vary significantly by race. In most epidemiological studies of psychiatric disorders, racial differences in the rates can be explained by socioeconomic and educational differences. The ECA was the first study in western society that permitted direct comparison of whites with blacks and Hispanics. Previous comparisons, which could not control for geographical differences, were subject to significant bias, because prevalence estimates clearly vary by place of residence.

LIFETIME PREVALENCE The overall lifetime prevalence of mood disorders from the ECA study is 6 percent. Distribution by age and gender is presented in Figure 16.2-3. Lifetime prevalence (which include current cases) follows a similar distribution as current rates. The lower lifetime prevalence of major depressive disorder in the elderly strongly suggests methodological problems and a significant cohort effect. One would expect that the longer a person lives (that is, the more years at risk for a psychiatric disorder), the more likely the person would experience that disorder.

A recent study of a national sample of over 8,000 persons from 15 to 54 years of age, the National Comorbidy Study estimates the prevalence rate of mood disorders to be higher than what was found in the ECA study. The current 30-day prevalence of major depressive disorder was estimated at 4.9 percent overall, and the lifetime prevalence was estimated at 17.1 percent. A different method of case ascertainment, however, rather than any change in actual prevalence since the ECA study, probably accounts for the higher estimates. The distribution of cases by sex and ethnic groups was similar to that found in the ECA study.

The findings of the ECA study and the National Comorbidity Study have tended to parallel earlier epidemiological studies in the United States, such as the Stirling County Study (current prevalence of major depression was 4.7 percent in men and 6.0 percent in women) and the New Haven Study (3.2 percent in men and 5.2 percent in women). Most studies in developed

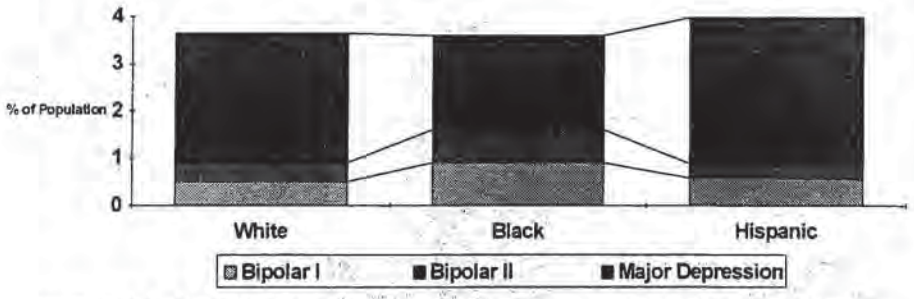
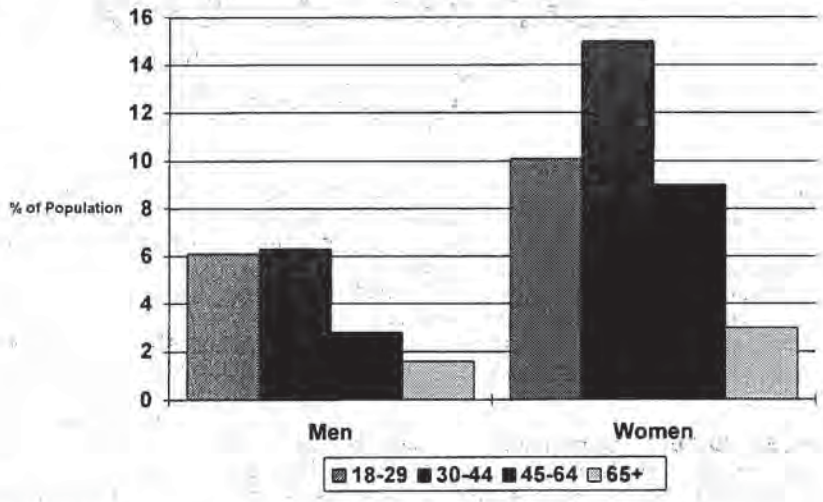


FIGURE 16.2-2 *Current (one year) prevalence of mood disorders by ethnicity. Data derived from the Epidemiologic Catchment Area study.*

FIGURE 16.2-3 *Lifetime prevalence of mood disorders by age and sex. Data derived from the Epidemiologic Catchment Area study.*



countries estimate the distribution of major depressive disorder to be greater in women than in men, in young adulthood than in midlife and old age, in urban residents than in rural residents, and among single or divorced persons than among married persons. Few studies document a racial difference when social class and education are controlled.

DEPRESSIVE SYMPTOMS The prevalence and distribution of clinically significant depressive symptoms parallels that of major depressive disorder, although the age differences are not nearly so great. In most studies, between 8 and 20 percent of community samples report depressive symptoms at a level above the cutoff used to screen for major depressive disorder, such as 16+ on the Center for Epidemiologic Studies Depression Scale (CES-D). Many of those persons do not meet criteria for specific DSM-IV mood disorders. Those depressive symptoms, however, have been associated with higher mortality rates, higher disability rates, and poor social functioning.

INCIDENCE The incidence of the mood disorders is the percentage of new cases of the disorder which emerge in a population at risk for the disorder (that is, persons not experiencing the disorder at the beginning of the study) over a specified period of time (usually one year). Because major depressive disorder is common and tends to remit and recur, the incidence is relatively high. The annual incidence of major depressive disorder in the ECA study was 1.59 percent overall. The distribution by age and sex is presented in Figure 16.2-4. A survey in Lundby, Sweden, revealed an annual first incidence of depression (cases of depression in persons who never experienced depression before) of 0.43 percent in men and 0.76 percent in women. Up to the age of 70, the cumulative probability of a first episode of depression was 27 percent in men and 45 percent in women, making depression one of the most important public health problems.

SETTING The prevalence of major depressive disorder is much higher in treatment settings than in the community at large. Most investigators find that 10 to 15 percent of persons in acute hospital settings and in long-term care facilities meet the criteria for the diagnosis of major depressive disorder. An additional 20 to 30 percent of persons in treatment settings report clinically significant, subsyndromal depression (minor depression). The similarities between those cases of major depressive disorder to cases found in psychiatric treatment settings has yet to be documented. Although some of the depressed and medically ill patients respond to antidepressant therapy and brief psychotherapy, many of them have comorbid conditions which render traditional therapies ineffective.

Depression is also more prevalent in primary care settings than in the general population. Using methods of case identification similar to the ECA study, the current prevalence of depression is about double that found in the general population. In most surveys of primary care clinics, over 20 percent of the patients report clinically significant depressive symptoms. Major depressive disorder is diagnosed in one third to one half of those outpatients—a prevalence of 5 to 10 percent. Young women are at greatest risk for depression in primary care, and

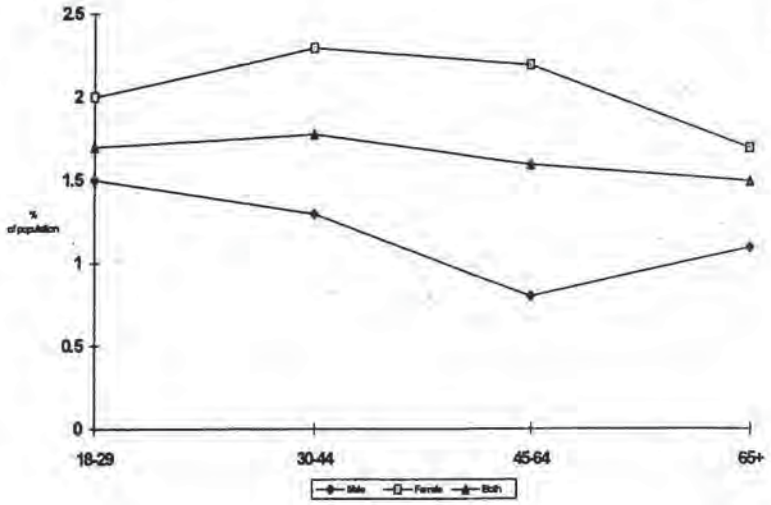


FIGURE 16.2-4 *Annual incidence of major depressive disorder by age and sex. Data derived from the Epidemiologic Catchment Area study.*

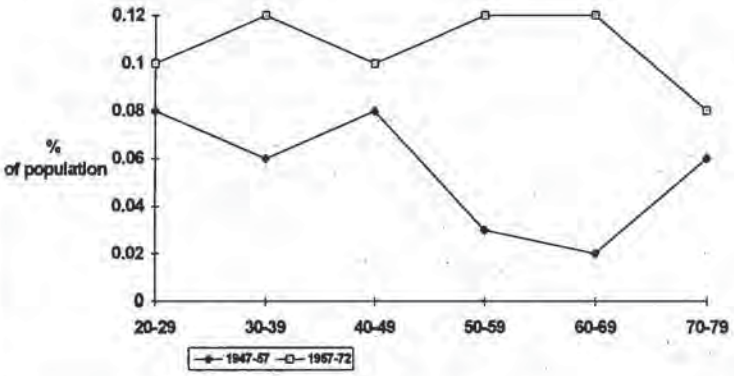


FIGURE 16.2-5 *Risk of contracting a first-onset depressive disorder for younger birth cohorts compared with older birth cohorts in Sweden. Data derived from O Hagnell, J Lanke, B Rorsman, L Ojesjo: Are we entering an age of melancholy? Depressive illnesses in a prospective epidemiological study over 25 years: The Lundby Study, Sweden. Psychol Med* 12: 279, 1982.

most persons who report depressive symptoms to a health care professional report them to a primary care physician. Unlike the depressive syndromes that present in hospital and long-term care settings, the depressive syndromes that present in outpatient medical settings may be prime targets for psychotherapeutic and pharmacotherapeutic treatment.

HISTORICAL TRENDS

The higher prevalence of depression in younger than in older age groups has led to the hypothesis that birth cohorts born after World War II are at appreciably greater risk for major depressive disorder than older birth cohorts in advanced Western society. The trend has been observed not only in the United States, but also in Sweden, Germany, Canada, and New Zealand. (Higher prevalence among older persons has not been observed in comparable community surveys in Korea, Puerto Rico, and Mexican Americans living in the United States.) When the findings were originally reported, many researchers attributed them to bias in case identification, such as problems of recall, selective mortality, and diagnostic criteria more applicable to a younger age. Thorough evaluation of the case finding methods, however, coupled with adjustments for selective mortality, do not substantiate bias as the sole explanation for the differences in prevalence across age groups.

A number of observations made prior to the ECA study suggested that rates of depressive disorders were changing. Relevant factors included a progressively lower age of onset of depressive disorders reported in community studies; an increase in childhood mood disorders seen by pediatricians and mental health workers; a decrease in deaths from suicide among the elderly; and a fall in the average age of onset for depressive disorders in clinical samples since World War II. For example, the risk of first-onset depression was higher for younger birth cohorts than for older birth cohorts in Sweden (Figure 16.2-5). The trends in suicide data parallel the trends in mood disorders (that is, suicide rates are much higher in younger persons today than they were 30 years ago, whereas suicide rates for older persons are lower today than they were 30 years ago (although suicide rates in older adults have increased by 25 percent since 1980).

FACTORS THAT INFLUENCE HISTORICAL TRENDS

Three factors influence the historical trends in the relative prevalence of mood disorders by age—period effects, age effects, and cohort effects.

Period effects *Period effects* are changes in the prevalence of an illness secondary to environmental stressors on the population, or particular age groups within the population, at a specific period in history. (For example, the uncertainty of employment among college graduates and the trend among younger persons to delay marriage during the 1990s may place young

adults at greater risk for depression and suicide because of economic impairment and lack of affiliative relations.)

Age effects *Age effects* are the biological and psychosocial factors that predispose an individual to develop a particular disorder during a specific part of the life cycle. (For example, the genetic predisposition to develop major depressive disorder is probably greatest during the 30s, whereas the predisposition to develop a bipolar disorder is greatest during the 20s.) Age-related changes in the brain, such as the increase in subcortical hyperintensities on brain magnetic resonance imaging, may also be associated with mood disorders. Perhaps the most consistent age effect relevant to the mood disorders that has been observed during the 20th century is the positive association between age and suicide among white males in the United States.

Cohort *Cohort effects* are the relative differences in rates of illness across different generations. The cohort is usually defined by the year or decade of birth. A person born in a given year may be at greater risk for an illness, such as major depressive disorder, throughout his or her life. Suicide data reveal marked cohort trends throughout the 20th century. (For example, persons currently 70 to 80 years of age [approximately the birth cohorts of 1915 to 1925] have exhibited lower suicide rates at all ages than the 1900 and 1940 birth cohorts.)

Interaction of effects There are considerable statistical and methodological problems in sorting out the relative contribution of period, age, and cohort effects upon the prevalence and incidence of mood disorders by age. First, those effects undoubtedly interact. Stressors during a particular period interact with age-related vulnerability. (For example, the current high rate of substance abuse among adolescents may be secondary, in part, both to the vulnerability of adolescents to substance abuse and to the greater availability of drugs to adolescents.) Second, older persons may not recognize major depressive episodes as such and so do not report them. Yet age does not appear to affect the rate of hospitalization for mood disorders. The more severe cases of major depressive disorder are hospitalized, regardless of age. The relative cohort differences persist in hospitalization rates.

Although most investigators have explained the current data as reflecting a cohort effect, some have suggested that they reflect a period effect. They argue that the risk for depressive disorders increased dramatically for all ages from about 1965 to 1975, but has since stabilized. Young persons are more vulnerable to that period effect, however, and therefore carry the greatest burden of depressive disorders. A young person who experiences a major depressive episode is likely to exhibit ongoing and severe depressive episodes for many years. Therefore, clinicians can expect to see the current cohort of younger persons bear the burden of major depressive disorder for a long time.

Despite being the healthiest and most affluent generation of the 20th century, younger persons may be at greater risk for major depressive disorder due to a number of environmental risk factors, including: (1) increased urbanization; (2) increasing social isolation and anomie; (3) changes in the roles of women; (4) changes in occupational roles and career trajectories for both men and women; (5) increased secularization; and (6) greater geographic mobility.

IDENTIFICATION OF CAUSES

The risk factors for bipolar disorders and major depressive disorder identified from epidemiological studies are summarized in Table 16.2-2. Some of the findings have not been replicated, but others have emerged repeatedly from both clinical and community-based studies. (For example, an increased risk for major depressive disorder was discovered in an isolated community of the Hutterites who live near the border between the United States and Canada, suggesting that the rigid moral control they exert predisposes community members to depression.) Most community studies, however, fail to find that identification with or participation in particular religious groups is associated with an increased risk for major depressive disorder. In contrast, virtually every community survey has demonstrated an increased risk for major depressive disorder and depressive symptoms in persons who report negative life events.

DEMOGRAPHIC FACTORS

Sex Almost all community-based epidemiological surveys of mood disorders find that women are twice as likely as men to be experiencing an episode of major depressive disorder. Few investigators discount the finding as an artifact of prejudice in the diagnostic criteria for major depressive disorder or of increased help-seeking behavior among women. Yet female sex has not been demonstrated to be a risk factor per se. The social environment of women and a higher threshold for reporting depressive symptoms in men may account for the increased association.

Age The average age of onset for both major depressive disorder and bipolar disorders falls between the ages of 20 and 40 years. Recent studies confirm that major depressive disorder can occur in childhood. Bipolar I disorder typically has an earlier age of onset than major depressive disorder, with an average of

TABLE 16.2-2
Risk Factors for Bipolar I Disorder and Major Depressive Disorder

Risk Factor	Bipolar I Disorder	Major Depressive Disorder
Sex	No difference	Women at greater risk than men
Race	No difference	Blacks at somewhat less risk than whites
Age	Young at greater risk	Young at greater risk
Socioeconomic status (SES)	Higher SES at somewhat greater risk	Lower SES at greater risk for depressive symptoms and for major depressive disorder
Marital status	Separated and divorced have highest rates	Separated and divorced have highest rates
Family history	Persons with family history have higher rates	Persons with family history have higher rates
Childhood experiences	Bipolar patients may come from families with low perceived prestige in their community	Evidence that early parental death and disruptive childhood environment leads to major depression
Stressful life events	No known difference	Negative stressful events associated with increased risk
Absence of a confidant	No known difference	Absence of confidant leads to increased risk, especially in women
Residence	Greater risk in suburbs than in inner city	Greater risk in urban areas than in rural areas

30 years. Yet both major depressive disorder and bipolar disorders can first occur at any time during adulthood. Nothing suggests that young age, in itself, places a person at greater risk for the mood disorders (though genetic factors may have their greatest influence at a younger age). Social factors appear to place younger persons at greater risk than the elderly. Biological predisposition to major depressive disorder may actually increase with age.

Race Race has not proved to be a significant risk factor for either bipolar I disorder or major depressive disorder. In many community surveys, blacks experience a higher prevalence of depressive symptoms. The racial difference usually disappears, however, when other factors, such as socioeconomic status, age, and residence, are controlled. Because treatment for mood disorders is less common for blacks than for whites, prevalence studies based on treatment samples usually contain proportionally more whites. Recent findings from the ECA study suggest that major depressive disorder may be less common among blacks than among whites and Hispanics. Investigators must not overgeneralize from these results, because the case finding methods used in the ECA study may be biased against finding cases among blacks. (For example, blacks may be more likely to somatize the experience of depression, although there was no evidence that blacks somatize overall more than whites.)

SOCIOECONOMIC STATUS The findings from community-based studies relating to socioeconomic status (SES) as a risk factor for depression are mixed. In the overall ECA studies, there was only a weak correlation between major depressive disorder or bipolar disorders and lower SES. In the North Carolina ECA study, however, there was a consistent relation between SES and major depressive disorder, even when multiple potential confounders, such as race and residence, were controlled. Studies prior to the ECA found a consistent positive relation between lower SES and depression. In one classic study reported by August Hollingshead and Fredrick Redlich, depressive symptoms were strongly associated with the lower social classes. In a more recent study, working-class women from an eastern suburb of London were much more likely to suffer depressive symptoms than women from higher social classes.

MARITAL STATUS Marital status appears to be one of the most consistent risk factors for both depressive symptoms and major depressive disorder. Rates for major depressive disorder are highest among separated and divorced persons, and lowest among single and married persons. Recent widowhood is associated with higher rates of major depressive disorder across the life cycle.

The risk appears to vary with sex. Single women have been found to have lower rates of depression than married women, whereas married men have lower rates than single men. However, the investigator must not confound marital status with the loss of a spouse through death or divorce (a stressful life event). If a subject was widowed during the six months prior to the study, then the event, not the status, is the causative factor. In addition, cause and effect may be reversed (for example, depressive illness may place a person at greater risk for divorce). In most studies, however, the separated or divorced status places the person at greater risk for depression, even if the marital breakup occurred long before the assessment.

The ECA studies, unlike previous studies, also documented a much higher prevalence of bipolar disorders among the separated and divorced than among single persons. The highest rates, however, were found among those who were cohabiting, even when adjusting for age, sex, and race or ethnicity. The association of the mood disorders and marital status is also reflected in the association of mood disorders with household size. Major depressive disorder is twice as common among persons living alone than among those who live with others. In persons not living alone household size is not associated with depression.

Marital status may not be the proximal causative factor. The perception of social support and lack of conflict within the social network are critical factors in protecting against mood disorders. Longitudinal studies of the social network and neuroses have shown that the most important predictors of depression are not the objective characteristics of the network, but rather the perception of how adequately the network assisted the person. Large-scale community-based investigations of the risk factors for major depressive disorder and bipolar I disorder cannot disentangle the subtleties of the complex interactions between persons and their social network. (For example, the dissolution of a difficult marriage may relieve long-standing depressive symptoms.)

FAMILY HISTORY Most epidemiological studies of treatment samples have shown a consistent increase in family history of mood disorders among subjects, especially in first-degree relatives. A family history of suicide and alcoholism has also been repeatedly demonstrated to be more common among the depressed subjects than among controls. Most experts attribute the increased risk for depression when family history is positive to a genetic predisposition. Yet the shared family environment may also contribute to the increased risk. Genetic transmission is much more firmly established for bipolar I disorder than for major depressive disorder. In family members of bipolar subjects, both bipolar I disorder and major depressive disorder are more prevalent.

EARLY CHILDHOOD EXPERIENCE Much attention has been directed to the association of early childhood experience with the onset of mood disorders later in life. Although the complexities of a psychodynamic investigation of childhood traumas cannot be applied in community-based epidemiological studies, even cursory investigation of childhood experiences has revealed correlates. Parental loss before adolescence has been well documented as a risk factor for adult-onset depression. A deprived and disrupted home environment also constitutes a risk. Methodological problems make objective study of childhood trauma and deprivation difficult. Some events, such as divorce or separation of parents, can be documented reliably, but others, such as parental neglect, are very subjective. The report of parental neglect by the depressed adult may vary depending on the respondent's emotional state at the time of the interview.

PERSONALITY ATTRIBUTES Personality attributes are closely related to early childhood experience as a risk for mood disorders in later life. Personality emerges early in life and is formed by biological tendencies coupled with the child's social environment. Persons predisposed to develop a depressive disorder have been shown to lack energy, to be more introverted, to worry, to be more dependent, and to be hypersensitive. Major depressive disorder has also been found to be frequently comorbid with the Axis II disorders. Yet the study of the relation of depression and personality is confounded by the time at which personality is studied. Epidemiologists rarely have the opportunity to assess personality before the onset of the first episode of depression. If personality is assessed during an epi-

sode of depression, then the depressive symptoms mask certain personality traits and exaggerate others. When a person has experienced and recovered from a depressive episode its impact on personality makes an accurate assessment of premorbid personality difficult. (For example, the personality characteristics that are associated with depression are exactly those which might emerge in response to the experience of a difficult mental disorder.)

SOCIAL STRESS Social stress has received more attention than most of the other risk factors for major depressive disorder across the life cycle. Three kinds of social stress can be distinguished: life events, chronic stress, and daily hassles. *Life events* are the kind most often used in epidemiological studies. They are identifiable, discrete changes in life patterns that disrupt the usual behavior and threaten the person's well-being. Bereavement, the stress reaction to the loss of a loved one, is the prototype stressful life event. *Chronic stress* includes long-term conditions that challenge the person, including financial deprivation, ongoing interpersonal difficulties (such as conflict in the workplace), and persistent threat to security (such as living in a dangerous neighborhood). *Daily hassles* are ordinary but stressful occurrences that are ubiquitous in modern life, such as managing household finances and unpleasant interactions with neighbors.

Life events Most epidemiological studies reveal a relation between stressful life events, especially negative events, and the onset and outcome of major depressive disorder. Nevertheless, the use of stressful life event scales, such as the Schedule of Recent Events, introduces many potential biases into the study of stressors and depression. Such scales usually tally the number of events and weight them according to a predetermined algorithm. Most schedules weight events based on normative data from the population. Because the data usually derive from weightings provided by young adults, they do not apply across the life cycle. (For example, retirement in late life may be a very positive event, whereas premature retirement in midlife may present major problems that can precipitate a depressive disorder.)

The perception of the event is probably more important than the event itself. More sensitive measures of stressful events document not only the event itself but the subject's response to it. Was the event perceived to be positive or negative? Even the death of a spouse may be viewed as a positive event if it occurred after a protracted and disabling illness during which the subject was the caretaker. Was the event perceived to be important or unimportant? For some older persons a move may be extremely traumatic, especially if it is the first move in half a century. For others, a move may be a usual and relatively unimportant event, especially in a society where mobility is becoming more the norm. Was the event expected or unexpected? If income decreases at retirement at a rate expected by the retiree, then the loss of income is much less stressful than if a person is forced to take an unexpected cut in salary while still in the workforce.

The accumulation of stressful negative life events does appear to predispose a person to episodes of major depressive disorder. In a study from New Haven, depressed patients had an average increased frequency of eight life events during the six months before the onset of depressive symptoms. Those events included marital arguments, marital separation, starting a new type of work, change in work conditions, serious personal illness, death of an immediate family member, serious illness of family members, and a family member leaving home. Stressful events are also associated with the persistence of depressive disorders. In a study from England, adverse events during the year following the initial episode of depression were associated with a poorer outcome of the episode. The adverse effects of life events may be offset by neutralizing events. (For example, if a woman loses her job but soon after finds another job with equal pay and benefits, then the adverse event is neutralized.) However, persons experiencing a recurrent major depressive disorder are less likely to report a stressful event associated with the onset of episodes after the first two episodes of depression.

Chronic stress Chronic stress can place a subject at greater risk for major depressive disorder than specific stressful life events. The stress of a chronic illness, for example, frequently manifests itself in the symptoms of a major depressive episode. As long as the stressor of the illness persists, the individual has difficulty recovering from the major depressive episode. Persons usually have more difficulty coping with ongoing stressors than with specific events, to which they can adapt.

Daily hassles Few studies document the association of daily hassles with the onset of major depressive disorder. Impulsive acts, such as a suicide attempt, may be closely associated with daily hassles to which the subject cannot adapt within the context of a stressful life event or chronic stress. That is, daily hassles may be the straw that breaks the camel's back.

SOCIAL SUPPORT Factors in the social environment that may modify the effects of social stress have received increased attention in the epidemiological investigation of both physical and psychiatric disorders. One factor is social support, the provision of meaningful, appropriate, and protective feedback from the social environment that enables a person to negotiate environmental stressors. In theory, social support is an attractive concept, for it is potentially more amenable to interventions than environmental stressors. The roots of the construct social support go back at least to the early 20th century, when Émile Durkheim proposed that persons who are not integrated into society (the condition called "anomie") are at greater risk for suicide.

Social support has four components: the social network, social interaction, perceived social support, and instrumental support. The *social network* consists of those individuals or groups of individuals, such as a spouse and children, who are available to the subject. The absence of a spouse is a risk factor for major depressive disorder. *Social interactions* may be assessed by documenting the frequency of interactions between the subject and other network members. A number of studies confirm that social isolation (that is, a deficit of social interaction) places a subject at greater risk for depression. Yet the quality of the interaction appears to be more important than the frequency of the interaction. *Perceived social support* is the subjective evaluation by the individual of the dependability of the social network, the ease of interaction with the network, the sense of belonging to the network, and the sense of intimacy with network members. The association of major depressive disorder and lack of a confidant is an example of the relation between perceived inadequate support and depression.

Instrumental support consists of concrete and observable services that are provided to the subject by the social network (for example, cooking meals, financial assistance, and nursing services for the physically ill). Although such support is essential to the well-being of the young and the elderly in society few studies document the association of depression with a deprivation of instrumental support. The physical health of the per-

son is a confounding factor. Instrumental support is usually not obvious unless the person exhibits an actual need for such services. In addition, the perception of the availability of those services in a time of crisis may not reflect the actual availability.

Social integration The construct of social support is strongly influenced by the construct of social integration. An integrated society is a social system which insures the patterns of interpersonal behavior that are essential to the survival and welfare of the society. Those patterns enable the group to obtain what is needed for subsistence, protection against weather and disease, control of hostility and other forms of social disruption, creation of new members and their education, disposal of the dead, communication, storage of information, and ways for arriving at decisions and taking united action. Alexander Leighton and his colleagues undertook the most ambitious epidemiological studies of social integration and mental health in a study of communities in Nova Scotia. Social scientists and anthropologists studied each community to determine its relative integration versus disintegration. At all ages, the rates of depressive disorders (and other psychiatric disorders) were higher in disintegrated communities. Studies of social integration are not as proximal to the individual as studies of social stressors and social support, because measures of social integration are not specific to the individual. Those studies are ecological, for they document that the overall level of social disintegration in a community is associated with the overall level of psychopathology.

Residence Most studies of social integration have been limited to comparisons of communities by traditional parameters, the most common of which is urban versus rural residence. The hypothesis is that rural communities are more integrated and less stressful than urban communities. In the ECA study of North Carolina, major depressive disorder was two times more common in the urban community, with the largest differences among the young (under 45 years of age) and among women. Those urban-rural differences in prevalence persisted even when the comparison was controlled for race, socioeconomic status, marital status, and age. The prevalence of major depressive disorder was also lower in North Carolina than in the other ECA sites, suggesting that geographical location may contribute to differences in the prevalence of major depressive disorder.

Unemployment Another risk factor for depression is unemployment. At present, most men and women under the age of 65 are in the labor force. Men and women who were unemployed for at least six months during the five years prior to the ECA survey were more than three times as likely as others to report the symptoms of an episode of major depressive disorder during the year prior to the survey.

The multiple risk factors for mood disorders form a web of causation. Each factor can not only affect the subject directly but can interact with other factors. Mathematical models of causative factors are therefore useful for determining the relative importance and the complex interaction of those factors. Models include linear and logistic regression analyses.

An example is presented in Table 16.2-3. Three variables in the multivariate model are significant—urban residence, younger age, and female sex. The coefficients in the logistic-regression model are equivalent to an odds ratio (that is, the odds of a risk factor being associated with major depressive disorder when the comparison factor has a risk of 1). For example, when the comparison factor for age is the over 65 age group, then the middle-aged (25 to 44) are over three times as likely to be depressed. Each of the risk factors is presented while accounting for the other factors (that is, all other factors are controlled).

TABLE 16.2-3
Logistic-Regression Effects (Odds Ratios) of Urban/Rural Residence and Control Variables on Major Depressive Disorder

Variable	Coefficient (Odds Ratio)	Significance
Urban residence	1.983	<.05
Age (25-44)	3.143	<.05
Separated or divorced	1.434	NS*
Widowed	0.738	NS
Never married	1.576	NS
Female	2.695	<.05
Nonwhite	1.130	NS
Education	1.033	NS
Moved in last 5 years	1.109	NS

*NS = Not significant

Table adapted from D G Blazer, L K George, R Landerman, M Pennybacker, M L Melville, M Woodbury, K G Manton, K Jordan, B Locke: Psychiatric disorders: A rural/urban comparison. Arch Gen Psychiatry 42: 651, 1985. Used with permission.

Therefore the risk for depression is increased in younger ages, even when education, marital status, and sex are taken into account.

PROGNOSIS

Two recent studies have concentrated on the public health impact of depressive disorders because of their chronic and disabling nature.

In the first, over 11,000 outpatients in a variety of primary care settings were screened for depression. Patients with either depressive disorders or depressive symptoms (without a diagnosis of a specific mood disorder) tended to have worse physical, social, and role functioning. When their objective health status was controlled, they perceived their current health to be worse than patients who were not depressed, and they reported greater physical pain. The poor functioning associated with depressive symptoms, with or without a diagnosis of a mood disorder or not, was comparable with or worse than in eight major chronic medical conditions. The number of days in bed with depressive symptoms was significantly greater than with hypertension, diabetes, or arthritis.

In a second study, from the ECA sample in North Carolina, persons with the diagnosis of major depressive disorder or dysthymic disorder and with symptoms of minor depressive disorder were followed for one year. Compared with asymptomatic individuals, persons with major depressive disorder had a five-times greater risk of disability and persons with minor depressive disorder had a one-and-one-half-times greater risk. Persons with minor depressive disorder were at greater risk of developing an anxiety syndrome and major depressive disorder at one-year follow-up.

Both studies demonstrate the need not to limit the cases in epidemiological investigations of depressive morbidity to existing nosological categories. They also demonstrate two key factors relating to the outcome of mood disorders in the community. First, depressive symptoms and major depressive disorder are important public health concerns. When distributing funds for research and clinical care, policymakers should recognize the costs of medical care, time lost from work, and the decreased life satisfaction associated with depressive disorders. The mood disorders are treatable despite their chronicity, and treatments have improved dramatically over the past 25 years. Yet the stigma of mental illness continues to affect coverage for the treatment of psychiatric disorders, and much less money is allotted for research on mood disorders than for many chronic and disabling illnesses that carry less stigma.

Second, the studies emphasize the risk among persons with less severe symptoms of developing more severe or additional psychiatric disorders, as well as to experience a poorer outcome from physical disorders. Mortality rates among the depressed are greater than among age-matched controls, even greater than are accounted for by suicide.

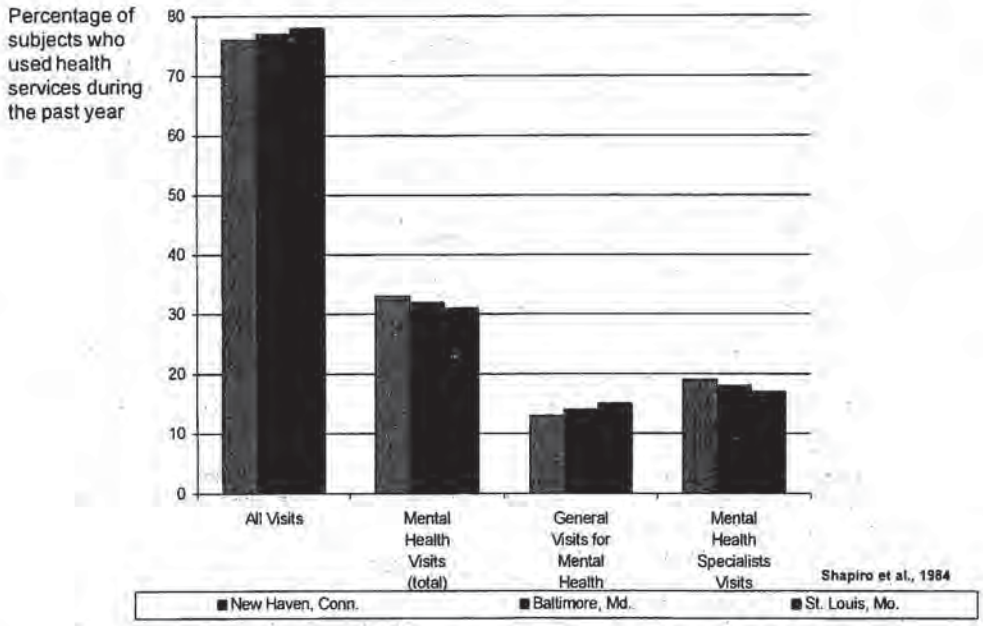


FIGURE 16.2-6 *Utilization of outpatients visits by persons with mood disorders (percentage use by category from three ECA sites).*

A number of natural history studies of mood disorders have been performed on clinical samples. The most extensively studied cohort derives from the Psychobiology of Depression Study of over 500 young adult and middle-aged subjects diagnosed with either bipolar I disorder or major depressive disorder. During the years following diagnosis, about 50 percent of patients recovered during the first year, but less than 30 percent of the others recovered during subsequent years. Comorbid dysthymic disorder with a slow onset, accompanying psychotic symptoms, and severe symptoms were associated with less likelihood for recovery. Relapse rates are high for major depressive disorder immediately following recovery. Superimposed dythymic disorder and a history of three or more major depressive episodes were associated with relapse. Bipolar I disorder patients with only manic episodes had a better outcome than those with major depressive disorder. However, bipolar I patients with a mixed episode (depression and manic) or with rapid cycling had a worse outcome than those with major depressive disorder.

USE OF HEALTH SERVICES

Use of health services for mood disorders occurs in general health care settings and in specialty settings. Most mental health visits reported by subjects in the ECA study, regardless of disorder, occur in primary care settings for older persons and in specialty settings for younger persons. Women use mental health services in both settings about twice as often as men. The pattern of mental health visits and general health visits at three ECA sites among subjects diagnosed with dysthymic disorder and major depressive disorder are presented in Figure 16.2-6. Visits are about equally distributed between general medical providers and mental health specialists in all three settings. All visits and all mental health visits are more frequent in persons who are depressed than for persons with no disorder identified in the ECA surveys.

SUGGESTED CROSS-REFERENCES

An overview of epidemiology is given in Section 5.1. Social origins of mood disorders are discussed in Section 4.2. Classification of mental disorders is presented in Chapter 11. Specific review of the genetics of mood disorders can be found in Section 16.4. The role of stress in the etiology of psychiatric disorders is discussed in Section 26.9. Suicide is discussed in detail in Section 30.1. The epidemiology of psychiatric disorders in late life is reviewed in Section 49.2.

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16.3
MOOD DISORDERS: BIOCHEMICAL ASPECTS

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

INTRODUCTION

The biochemistry of affective disorders, called mood disorders in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), has been an active area of scientific investigation since the introduction of the first clinically effective antidepressant drugs—imipramine (Tofranil) and the monoamine oxidase inhibitors (MAOIs)—in the late 1950s. In the decades since then, those first antidepressant drugs, as well as the newer ones as they have come along, have themselves become major research tools. Research into their mechanisms of action has provided the basis for various working hypotheses about the biochemistry of depressions and has led to more fundamental discoveries about the neurobiology of the central nervous system (CNS) itself. This section delineates the several lines of current research on the biochemistry of depressive disorders and provides a guide for understanding existing theoretical frameworks.

The brain contains 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 (a 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, and 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. This interaction may produce electrical stimulation (increasing the likelihood of an action potential) or electrical inhibition (decreasing the likelihood of an action potential) of the postsynaptic neuron, as well as intracellular biochemical and physiological changes within the postsynaptic neuron.

Many different substances apparently can act as neurotransmitters in the brain, and many other brain chemicals can be regulators or modulators of the process. Pharmacological agents, such as the antidepressants or environmental stimuli of many kinds, ultimately exert their effects by altering neurotransmitter-mediated or neuromodulator-mediated interactions between neurons.

Genetic factors may have biochemical expressions at the synapse, and environmental or psychological factors may act in that way as well. Neurochemical and neurophysiological changes secondary to such factors can alter a person'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 and neurophysiological changes are probably involved to a greater or lesser degree in virtually every type.

Most biological research involving the mood disorders aims ultimately at learning more about the workings of the CNS in these disorders. As an offshoot of that research, however, investigators are utilizing various biochemical measures in an attempt to subtype the mood disorders. Biological subtyping, if successful, may allow the differentiation of groups of patients who appear similar clinically but differ biochemically. The existence of such subtypes may have important clinical implications.

HISTORY

The two major classes of antidepressant drugs, the MAOIs and the tricyclic antidepressants, were first used in psychiatry nearly 40 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 (norepinephrine, epinephrine, and dopamine) or indoleamines (such as serotonin), two of the many groups of chemical substances that function as neurotransmitters within the CNS. One of the

catecholamines, norepinephrine, seemed to have particular importance in that regard. The first clue was that the MAOIs increased concentrations of norepinephrine in the brain by blocking one of its metabolic pathways. Shortly thereafter the drug imipramine, a tricyclic antidepressant, was found to enhance the effects of norepinephrine by blocking a major inactivation mechanism—the reuptake of norepinephrine into presynaptic neurons after release into the synaptic cleft. At about the same time reserpine (Serpasil), a drug then used for hypertension, was noted 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 by Joseph Schildkraut in the mid-1960s. In its simplest form, the hypothesis 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 may be associated with an excess of such catecholamines. The focus on levels of catecholamines in the simplest statement of the hypothesis was based on the research techniques of the day, which only allowed for the measurement of the output and metabolism of norepinephrine released by presynaptic neurons. Nevertheless, the possibility of abnormalities in receptor function was also considered in the general formulation of the hypothesis, because it was known that in the event of receptor subsensitivity a relative functional deficiency of norepinephrine could occur even with normal or elevated presynaptic output.

Because the broad clinical and biological heterogeneity of depressive disorders was recognized, it was apparent from the outset that a 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, and 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 raised in the initial formulation of the catecholamine hypothesis of affective disorders. Subsequent studies by many research groups provided considerable data to support this possibility. Other research has looked at the role of other neurotransmitters, neuromodulators, and neurohormones in patients with mood disorders. For example, there have been numerous studies on the relationship of serotonin, dopamine, acetylcholine, and corticotropin-releasing hormone (CRH) to the mood disorders.

In the past, many investigations attempted to separate the depressive disorders into noradrenergic or serotonergic depressions, according to certain biochemical data and particular responses to various tricyclic antidepressant drugs. This approach, 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, and data on the physiological interactions between noradrenergic and serotonergic neurons and the complex neuropharmacological effects of antidepressant drugs, make it obvious that such separations are overly simplistic and artificial.

Acetylcholine, another classic neurotransmitter, also may play a role in the pathophysiology of certain 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. Recent studies have also suggested that some depressed patients may have supersensitive acetylcholinergic receptors. Thus, the anticholinergic effects of the commonly prescribed antidepressant drugs may be responsible for more than side effects; they may be of some importance in the drug's actual antidepressant effects 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 have been investigated in many laboratories throughout the world.

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. In particular, the close connection to the endocrine system has become increasingly clear over the past 25 years. Many specialized laboratory tests are now being used in psychiatry, and it is expected that such clinical laboratory tests will play an increasingly important role in the diagnostic evaluation and treatment of patients with depressive disorders.

BIOGENIC AMINES

The term "biogenic amine" generally refers to four compounds—the catecholamines norepinephrine, epinephrine, and dopamine and the indoleamine serotonin. All four compounds have a single amine group on the side chain and consequently are also called monoamines. The neuronal systems utilizing the monoamines originate as relatively small collections of cell groups located mainly in the brainstem. From there the cell groups project widely into other brain regions, where they regulate neuronal processing of information and the tone and coloring of behavior. The widespread projections of these neuronal systems make them logical targets for psychiatric research, since small changes in them can have diverse behavioral effects.

At the synapse, the biogenic amines are released into the synaptic space and act at presynaptic and postsynaptic receptor sites. Most of the neurotransmitter is inactivated by reuptake into the presynaptic neuron; however, a portion may be metabolized outside the neuron after release into the synaptic space. The mitochondrial enzyme monoamine oxidase (MAO) is involved in the metabolism of neurotransmitters within the presynaptic neuron; such intraneuronal metabolism of neurotransmitter can occur independent of neurotransmitter release into the synaptic cleft.

NOREPINEPHRINE METABOLISM AND PHYSIOLOGY

The noradrenergic cell bodies containing norepinephrine are found in the locus ceruleus, 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 brainstem nuclei, and spinal cord. Individual locus ceruleus neurons can simultaneously send collateral branches to the neocortex, hippocampus, cerebellum, and spinal cord. The norepinephrine projections from the locus ceruleus also regulate brain blood flow and capillary permeability.

Many lines of evidence suggest that some patients with depressive disorders have abnormalities in catecholamine physiology or metabolism. Studies in animals have shown that many clinically effective antidepressants alter the reuptake, metabo-

lism, and turnover of norepinephrine in the brain. Recent longitudinal clinical studies measuring norepinephrine and its metabolites in the urine of depressed patients during six weeks of treatment with the antidepressant desipramine (Norpramin) showed that desipramine produces time-dependent changes in the metabolism and turnover of norepinephrine, which may help to explain the well-known two- to six-week lag time in clinical response to antidepressant drugs. Total norepinephrine synthesis and turnover were decreased during the entire course of treatment with desipramine, as reflected in sustained decreases in urinary levels of the major deaminated O-methylated metabolites of norepinephrine, 3-methoxy-4-hydroxymandelic acid (VMA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), that in part reflect intraneuronal metabolism by MAO (see above). By contrast, urinary norepinephrine and its O-methylated metabolite normetanephrine, which are derived from physiologically active norepinephrine released extraneuronally into the synaptic space, were decreased during the first week of treatment with desipramine but increased in subsequent weeks. These data suggest that the clinical response to desipramine may be related in part to an increased release of norepinephrine extraneuronally (that is, into the synapse) that occurs after the first week of treatment.

Tyrosine hydroxylase is the rate-limiting enzyme in the biosynthesis of norepinephrine, and recent evidence suggests that this enzyme may be involved in the pathophysiology of depression. For example, one recent study reported decreased levels of tyrosine hydroxylase protein in the brains of suicide victims. Another study noted that administration of α-methylparatyrosine, an inhibitor of tyrosine hydroxylase, produced an exacerbation of symptoms in patients whose depression had been improved by antidepressant treatment with the norepinephrine reuptake inhibitors desipramine and mazindol (Mazanor, Sanorex).

One method of studying the activity of noradrenergic neurons in the brain of living patients is to measure the level of MHPG in the urine. Known to be a major metabolite of norepinephrine originating in the brain, MHPG also derives in part from the peripheral sympathetic nervous system. MHPG from either source may undergo conversion to VMA. Thus, the fraction of urinary MHPG that is derived from brain norepinephrine is uncertain. Despite that 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.

Urinary MHPG levels In longitudinal studies of patients with naturally occurring classic bipolar (manic-depressive) disorder or amphetamine-induced manic-depressive episodes, many investigators have found that under antidepressant drug-free conditions, levels of urinary MHPG are 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 observation 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 classic bipolar manic-depressive depressions than in patients with unipolar nonendogenous chronic characterological depressions. Subsequent studies confirmed the presence of reduced urinary MHPG levels (and plasma norepinephrine levels) in patients with classic bipolar depressions—that is, bipolar I (but not bipolar II) depressive disorders—when compared with mean values in patients with various subtypes of unipolar depression, including major depressive disorder, or in nondepressed control subjects. One study suggested that the differences in urinary MHPG levels between patients with bipolar depression and control subjects became more pronounced when the peripheral contribution to urinary MHPG was reduced with carbidopa (Sinemet), a decarboxylase inhibitor that does not cross the blood-brain barrier.

In contrast to the reduction in urinary MHPG levels in depressed patients with bipolar disorder as compared with unipolar depressive disorder, a number of studies reported no differences in urinary VMA levels. This finding is important, because 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.

A wide range of plasma norepinephrine, plasma MHPG, and urinary MHPG levels have been reported in patients with unipolar depressions, including major depressive disorder. Low, intermediate, and high levels of urinary MHPG have been found in various studies. The range of findings may be due to diagnostic heterogeneity among patients with major depressive disorder and other unipolar depressions: In some patients levels of urinary MHPG are as low as those seen in patients with bipolar disorder; in others values are sometimes above the normal range. Because urinary MHPG values in normal control subjects also tend to exhibit a broad range, they cannot be used to diagnose depression per se but may help in the differentiation of depressive subgroups.

Recent studies have described a subgroup of patients with severe unipolar depressive disorder in whom urinary MHPG and urinary free cortisol (UFC) levels were both very high. In this subgroup of severely depressed patients with high catecholamine and cortisol output, increased acetylcholinergic activity could conceivably be a primary factor in the depression, with elevated urinary MHPG and UFC levels as a secondary response. This suggestion is particularly intriguing when certain other data are considered: (1) physostigmine (Antilirium, Eserine), an anticholinesterase, and other pharmacological agents that increase brain cholinergic activity exacerbate depressive symptoms in normal control subjects; (2) physostigmine produces an increase in plasma cortisol levels in normal controls; (3) physostigmine can overcome suppression of the hypothalamic-pituitary-adrenocortical (HPA) axis by dexamethasone in normal subjects, thereby mimicking the abnormal escape from dexamethasone suppression seen in some depressed patients with cortisol hypersecretion; and (4) physostigmine produces an increase in cerebrospinal fluid (CSF) levels of MHPG in healthy subjects. These observations have led to speculation about a possible adrenergic-cholinergic imbalance in some depressed patients and raise the possibility that the anticholinergic effects of some antidepressant drugs, commonly regarded as side effects, may actually contribute to their antidepressant action in patients with this depressive subtype.

There may be at least three distinct subtypes of what appear to be unipolar depressive disorder that can be distinguished by urinary MHPG levels. Subtype I, characterized by 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 subtype I may be patients with underlying bipolar I [manic-depressive] disorders who have not yet experienced a first episode of mania or hypomania.) In contrast, subtype II, characterized by intermediate urinary MHPG levels, may have normal norepinephrine output but abnormalities in other biochemical

systems. Subtype III, characterized by high urinary MHPG levels, may have high norepinephrine output in response to alterations in noradrenergic receptors, an increase in cholinergic activity, or an increase in CRH activity (described below). Further research is required to confirm these findings and to explore physiological abnormalities that may be associated with the different subtypes of unipolar depressive disorder.

D-type equation Although MHPG levels alone help differentiate subtypes of depression, multivariate discriminant function analysis has been used to explore the possibility that the inclusion of levels of norepinephrine (NE), epinephrine (E), normetanephrine (NMN), metanephrine (MN), and VMA might provide an even better differentiation. This analysis led to the development of an empirically derived equation, termed the depression-type (D-type) equation, that distinguishes even more precisely between depressed patients with classic bipolar (manic-depressive) disorder and unipolar nonendogenous chronic characterological depression than urinary MHPG alone. The discrimination equation is of the form:

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

The metric for the equation was established so that patients with bipolar depressions would tend toward a score of 0 and patients with unipolar nonendogenous depressions would tend toward a score of 1.

In a subsequently studied validation sample of 114 depressed patients whose data had not been used to derive the equation, the D-type score (using a criterion of D-type score ≤ 0.5) had a sensitivity of 0.85 and a specificity of 0.83 in identifying depressed patients with clinically diagnosed bipolar (manic-depressive) disorder and bipolar-related schizoaffective depressions. A wide range of D-type scores was seen in patients with clinically diagnosed (putative) unipolar endogenous depressions (that is, depressed patients with no prior history of mania). Preliminary findings using the equation suggest that low D-type scores in patients with such putative unipolar depressions may identify patients with latent bipolar disorders who have not yet had a clinical episode of mania.

D-type scores may be an even better predictor than urinary MHPG levels alone of responses to imipramine or alprazolam (Xanax) in patients with unipolar depressions. When a model or equation that was derived to describe or account for observations in one domain is found to have more general applicability in predicting observations in another domain, confidence in the explanatory power of that model is enhanced. The D-type equation was initially derived to separate depressed patients with bipolar (manic-depressive) depressions from depressed patients with other subtypes of depressive disorders. The finding that D-type scores also appear to predict differential clinical responses to certain antidepressant drugs in patients with unipolar depressions thus extends the potential clinical utility of the D-type equation, and also enhances its heuristic value.

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 help predict responses to certain tricyclic and tetracyclic antidepressant drugs. In many, though not all, studies depressed patients with low pretreatment urinary MHPG levels have been found to respond more favorably to treatment with imipramine, desipramine, nortriptyline (Pamelor), or maprotiline (Ludiomil) 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 or alprazolam than do patients with lower MHPG levels. As noted above, D-type scores may be a better predictor of response to some antidepressant drugs than urinary MHPG levels alone. Further research is required.

Urinary MHPG values trichotomized into the three subtypes described above may be useful in predicting treatment responses. Preliminary data have shown 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 was as responsive as patients with low MHPG levels. Moreover, patients with low pretreatment urinary MHPG levels responded rapidly to relatively low doses of maprotiline, whereas those with elevated MHPG levels required significantly higher doses and longer periods of drug administration, if they responded to maprotiline at all. This finding suggests a differential response, or that the antidepressant drug maprotiline may exert different pharmacological properties in high doses than in low doses. The concept 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.

At present, it is not possible to draw valid inferences about biochemical predictors of differential antidepressant drug responses on the basis of hypothesized pharmacological mechanisms of action, as it is known that antidepressant drugs have multiple, complex effects on many neurotransmitter systems. Consequently, empirical clinical trials are needed to assess the value of particular biochemical measures, such as urinary MHPG levels, as clinically useful predictors of responses to each specific antidepressant drug. But because the patients referred for study in academic centers today may be more refractory to the commonly used antidepressant drugs than the patients studied some years ago, when antidepressant drugs were less widely used in medicine and psychiatry, caution must be exercised when comparing new data with earlier findings.

DOPAMINE METABOLISM AND PHYSIOLOGY A role for dopamine in the pathophysiology of depression is suggested by the fact that certain antidepressant drugs produce effects on dopaminergic systems. More direct evidence that dopamine is involved in depressive pathophysiology comes from studies of homovanillic acid (HVA), the major metabolite of dopamine, in patients with mood disorders. Studies have found that levels of HVA in the CSF are reduced in many depressed patients (especially those with psychomotor retardation and suicidality) compared to controls. However, depressed patients with delusions of a history of psychosis may have higher CSF HVA levels than patients with nonpsychotic depressions. An increase in dopamine turnover in response to increased corticosteroid output has been proposed as a mechanism that could account for the increased CSF HVA levels in patients with delusional depressions.

SEROTONIN METABOLISM AND PHYSIOLOGY The cell bodies of serotonergic neurons are located in the raphe nuclei and superior central nucleus, and their axons project widely throughout the CNS—to the entire neocortex, rhinal cortex, thalamus, hypothalamus, limbic structures, reticular formation, locus ceruleus, cerebellum, and spinal cord. As for noradrenergic neurons, the widespread projection of serotonergic neu-

rons makes them logical candidates for psychiatric research. In many regions the serotonergic and noradrenergic projections overlap with each other, and there is at least one major interface between the raphe nuclei of the serotonergic system and the locus ceruleus of the noradrenergic system.

Certain lines of evidence suggest that some patients with depressive disorders have abnormalities in serotonin physiology or metabolism. Studies in animals have shown that treatment with many clinically useful antidepressants alters the reuptake, metabolism, and turnover of serotonin in the brain. And in depressed patients, successful treatment with serotonin-specific reuptake inhibitor (SSRI) antidepressants may be reversed by consumption of a diet augmented with neutral amino acids, which block transport of tryptophan, the amino acid precursor of serotonin, into the brain.

A number of studies have found that some depressed patients have reduced levels of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of brain serotonin, in the CSF. Other studies have noted an association between low CSF 5-HIAA levels and an increased incidence of completed suicide, attempted suicide, or impulsive acts of aggression. Among unipolar depressed patients, those who attempt or complete suicide often have lower CSF 5-HIAA levels than those who are not suicidal.

Reduced concentrations of serotonin or 5-HIAA have been found in postmortem brain tissue taken from depressed and suicidal patients. Some, but not all, studies looking at the brains of suicide victims have found that the binding of tritiated (H^3)-imipramine, which binds to reuptake sites on presynaptic serotonergic nerve terminals, is decreased. Moreover, some but not all studies have found increased postsynaptic 5-hydroxytryptamine (5-HT_2) serotonin receptor densities in the brains of suicide victims. Taken together, these findings have led a number of investigators to suggest that there may be a serotonin deficiency in suicide victims or in depressed patients who attempt suicide.

Decreased serotonin uptake into platelets has been observed in patients with depressive disorders. H^3-imipramine binds to serotonin uptake sites in platelets as well as brain, and a highly significant decrease in the number of H^3-imipramine-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. While it has been proposed that the decreased platelet H^3-imipramine binding observed in depressed patients may reflect a deficiency in the platelet serotonin transport mechanism in those patients, recent studies employing H^3-paroxetine cast some doubt on this proposal. Paroxetine is a more specific ligand than imipramine for labelling the serotonin transporter protein. And in several recent studies, there was no difference in the binding of H^3-paroxetine in platelets when values in depressed patients and control subjects were compared.

Another research strategy for evaluating serotonin physiology in depressed patients involves the use of challenge tests in which the endocrine responses to serotonin-releasing agents, such as fenfluramine (Pondimin), or to serotonin receptor agonists are evaluated. These studies have suggested that the primary abnormality of serotonin neurotransmission in depression may be decreased serotonin release rather than altered sensitivity of postsynaptic serotonin receptors.

Last, the introduction in recent years of new antidepressant drugs (fluoxetine [Prozac], sertraline [Zoloft], and paroxetine [Paxil]) that are relatively specific blockers of serotonin reuptake into presynaptic nerve terminals has highlighted the importance of serotonin systems in the pathophysiology and treatment of depression. Further studies are required to elucidate whether the specific serotonin reuptake blocking drugs have a mechanism of action that is truly distinct from that of older agents or whether the drugs all share one or more common pathways of action.

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

Receptors are studied by in vivo or in vitro techniques. In vivo study involves the use of pharmacological challenges to affect physiological processes thought to reflect the action of particular receptors. For example, the α_2-adrenergic receptor agonist clonidine (Catapres) stimulates growth hormone (GH) release, which is thought to occur via the postsynaptic α_2-adrenergic receptor. In many depressed patients the GH response is blunted, suggesting decreased sensitivity of these receptors.

Direct studies of brain receptors have been performed on postmortem tissue. The finding of increased serotonin 5-HT_2 receptor density in the brains of suicide victims was discussed earlier. There have also been studies of noradrenergic β- and α-receptors in various regions of the cortex and in subcortical regions of the brain. Although the findings are of interest, to date they are not consistent and thus do not allow definitive interpretation. Clearly, additional research in this area is required.

The study of adrenergic receptors on human blood cells allows in vitro measurement of adrenergic receptors from psychiatric patients. These receptors may not reflect similar changes in the CNS; however, they do provide a valuable research tool. For example, the number of β-adrenergic receptor binding sites on lymphocytes has been found to be decreased in some depressed and manic patients compared to control subjects or euthymic patients. Some studies also suggest that β-adrenergic receptor-mediated stimulation of cyclic adenosine monophosphate (cAMP) production by isoproterenol (Isuprel) is reduced in leukocytes and lymphocytes from depressed patients. One investigator noted a lack of responsiveness in depressed patients with psychomotor agitation but not in those with psychomotor retardation. More research is needed to clarify the significance of findings suggesting decreased β-adrenergic receptor function in lymphocytes from some depressed patients.

There also have been studies of platelet α_2-adrenergic receptors, which suppress the activity of prostaglandin-stimulated adenylate cyclase, in depressed patients. Some studies of depressed unipolar patients with depressive disorder have reported that both prostaglandin-stimulated and α_2-adrenergic suppression of prostaglandin-stimulated adenylate cyclase were decreased, while other studies have reported platelet adenylate cyclase (whether basal, prostaglandin-stimulated, or α_2-adrenergic suppression of prostaglandin-stimulated) to be unchanged. The discrepancies between these sets of observations may reflect differences in platelet adenylate cyclase activity in subgroups of depressed patients.

Several studies have reported that the total numbers of platelet α_2-adrenergic receptors were either unchanged or increased (but not decreased) in depressed patients. In light of the findings of decreased platelet α_2-adrenergic suppression of adenylate cyclase, the failure to find a decrease in the number of platelet

α_2-adrenergic receptors suggests a defect in the coupling between platelet α_2-adrenergic receptors and platelet adenylate cyclase in some patients with unipolar depressive disorder. This deficiency may involve the guanine nucleotide regulatory proteins that link neurotransmitter or hormone receptors to the catalytic unit of adenylate cyclase.

Thus, the evidence suggests that depressive disorders may be associated with a decrease in the absolute number or function of a diverse range of adrenergic receptors. Also, several laboratories have found increased catecholamine output in some depressed patients. In the presence of increased catecholamine levels, catecholamine-receptor interactions tend to become desensitized over time. One group of investigators has suggested that the changes in receptor coupling and functioning seen in some depressed patients may be the result of heterologous desensitization. The term "heterologous desensitization" (or agonist-nonspecific desensitization) refers to the process whereby long-term exposure to one particular agonist (such as a neurotransmitter, neuromodulator, or hormone) produces diminished responsiveness to multiple agonists in many different receptor systems because of a reversible alteration in the guanine nucleotide regulatory proteins that link or couple all of those receptors to the catalytic unit of adenylate cyclase. This concept raises the possibility that many of the physiological and neuroendocrine-metabolic alterations observed in patients with depressive disorders (including some of the psychoneuroendocrine abnormalities described below) may be the result of catecholamine-induced heterologous desensitization.

PLATELET MAO ACTIVITY To explore further the pathophysiology of the depressive disorders, investigators have studied the enzyme MAO, which deaminates biogenic amines in many body tissues, including the nervous system and the blood platelet. A growing body of literature suggests that levels of platelet MAO activity may help discriminate among subtypes of depressive disorders.

In the early 1970s platelet MAO activity was reported to be increased in a heterogeneous group of depressed patients (most of whom had unipolar depressive disorder) and to be decreased in a group of bipolar depressed patients. Subsequent results have not been as clear. For example, some investigators have 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 and different methods to determine platelet MAO activity, it is not possible to reconcile the conflicting data at the present time.

One study, however, suggested that bipolar disorder and unipolar depressive disorder may show differences in the relation between platelet MAO activity and the severity of clinical symptoms. In bipolar depression greater severity was associated with low platelet MAO activity, and in unipolar depression greater severity was associated with high platelet MAO activity. (That study systematically excluded patients with schizotypal features, such as unusual perceptions, ideas of reference, impairment in communication, and a history of social isolation. This was done because the presence of such schizotypal features would raise the question of schizophrenia-related disorders, with associated changes in platelet MAO activity, which might otherwise confound the data.)

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

In some studies of patients with unipolar depressive disorder platelet MAO activity correlated both with the severity of the depression and with anxiety symptoms and somatic complaints. The clinical items that correlated with platelet MAO activity in these studies corresponded to symptoms reported by other investigators to be associated with favorable responses to treatment with MAOIs. Other studies have found an association of high platelet MAO activity with social introversion or asociality and of low platelet MAO activity with social extraversion or sensation-seeking.

Despite the interesting data about platelet MAO activity, further research needs to be done. For example, additional studies are 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. Research is also needed to compare kinetic parameters (and other properties) of platelet mitochondrial MAO with other biological indices in patients with various subtypes of depressive disorders and in control subjects. Recently developed molecular genetic strategies for studying the MAO enzymes should be used to help elucidate the possible linkage of MAO genes to various subtypes of mood disorders and to explore the mechanisms by which those genes are regulated by neurotransmitters, hormones, and other neuroregulators.

PSYCHONEUROENDOCRINOLOGY

Because many endocrinopathies present with psychiatric symptoms, particularly affective symptoms, clinicians and investigators have long considered the possible connection between the endocrine system and mood disorders. The discovery that peptides from the hypothalamus, under the control of various neurotransmitters linked with the pathophysiology of these disorders, regulate the release of pituitary hormones prompted further speculation about this relationship. Recent advances, including the development of sensitive hormonal assays and the isolation of many hypothalamic peptides, have enabled psychoneuroendocrinology to emerge as an important research discipline.

The possibility that hormones might be related to affective states was raised 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 a mediator of behavior, however, was unclear for years. It was not until the late 1940s that the neurovascular model linking the hypothalamus and the pituitary was first proposed, and 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)—and later corticotropin-releasing hormone (CRH)—but its structure eluded investigators until 1981. In the past 20 years a number of hypothalamic peptides controlling the anterior pituitary have been isolated and synthesized, among them thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), growth hormone-releasing factor (GHRF), growth hormone release-inhibiting factor (GHRIF or somatostatin), and CRH itself.

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 the hypothalamus, 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: the search for one or more laboratory tests of endocrine function that might distinguish certain affective subtypes from other subtypes of mood disorders, or mood disorders 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 of that release by circulating target organ hormones, and an overriding control on the entire system by internal biological rhythms or external events affecting the hypothalamus.

The methods used for studying the endocrine network as it relates to mood disorders are multifaceted. First, because each bodily hormone is released according to a circadian rhythm, the study of possible changes in rhythm in an affective disease state is of interest. Second, the response of the anterior pituitary to the introduction of a hypothalamic factor can also be measured in affected patients and compared with normal subjects. Third, direct challenges to the hypothalamus itself, such as insulin-induced hypoglycemia, provide further information about the functioning of the endocrine axes. Fourth, provocative neuropharmacological challenges with such drugs as the 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. The studies are often conflicting, yet one conclusion seems sure: Various endocrine changes are associated with affective disorders. The best-documented changes involve the hypothalamic-pituitary-adrenal (HPA), the hypothalamic-pituitary-thyroid (HPT), and the hypothalamic-pituitary-growth hormone (HPGH) axes.

The material below details particular disturbances. Most of the work has involved patients with unipolar (including major) depressive disorder, but studies on patients with bipolar disorder are noted where applicable. Because the field is changing rapidly, the material is best read as a guide to the status of the field in mid-1994.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS CRH, the hypothalamic neuropeptide identified in 1981, is the principal regulator of ACTH release from the anterior pituitary and exerts a stimulatory effect on ACTH release. ACTH in turn stimulates the synthesis and release of cortisol from the adrenal cortex. Cortisol feeds back to inhibit the release of both CRH from the hypothalamus and ACTH from the pituitary. An additional, important point of regulation involves feedback of cortisol to the hippocampus, which exerts a tonic inhibitory effect on CRH release. The entire HPA axis has a circadian rhythm; most of the cortisol released from the adrenal glands comes in periodic bursts in the early morning hours.

CRH has been a focus of intense research interest over the past decade. Primarily, this interest stems from the discovery that CRH is widely distributed in the brain outside of the hypothalamus and has neurotransmitter function independent of its role in the HPA axis. High concentrations of CRH are found in the neocortex, limbic system, and regions involved in regulation of the autonomic nervous system; CRH receptors are also found in high concentration near the locus ceruleus. CRH activates the peripheral sympathetic and adrenomedullary systems, increases both norepinephrine and dopamine turnover throughout the brain, and produces behavioral changes in experimental animals similar to those seen following stress; these changes are generally independent of the effects of CRH on the HPA axis. These latter observations have led some investigators to propose that CRH is a central integrative mediator of the stress response. CRH release from the hypothalamus is itself stimulated by noradrenergic, serotonergic, and cholinergic inputs and is inhibited by γ-aminobutyric acid (GABA). The reciprocal interactions between CRH and catecholaminergic systems and the complex central functions of this neuropeptide make it a natural candidate for consideration as a factor in psychiatric pathophysiology.

Corticoid levels in depression Hypersecretion of cortisol, documented by 24-hour urinary corticoid output or serum cortisol levels, has been consistently reported in depressed patients over the past two decades; such abnormalities are found in approximately half of the depressed patients studied. The cortisol hypersecreters show a characteristic flattening of the 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 and not merely due to stress or hyperactivity. In most studies the hypercortisolic state has been reported to revert to normal with clinical remission, although one study suggested that in some depressed patients elevated urinary cortisol levels may persist after resolution of the depression. Interestingly, plasma cortisol levels in depressed patients at one-year follow-up have been found to predict poor social and occupational functioning, independent of the degree of residual depression.

Dexamethasone suppression test The dexamethasone suppression test (DST) has been used extensively to study the HPA axis in patients with affective disorder. First introduced in 1960 for the study of Cushing's disease, the 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 results (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. Those reports specified (1) an optimal method (1 mg of oral dexamethasone, with 4 PM and 11 PM plasma cortisol measurements); (2) sensitivity (67 percent); (3) specificity (96 percent, if strict exclusion criteria are followed); and (4) a cutoff for normal postdexamethasone plasma cortisol levels (5 μg/dL). Some recent studies have reported data utilizing other dexamethasone dosages; a few investigations have suggested that a 2-mg dose may provide a more valid measure of the cortisol hyperactivity.

The more recent literature contains many reports both confirming and questioning various aspects of the early DST findings. The reported sensitivity level for the 1-mg dose 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 or in older depressed patients has been found to be higher than

in nonpsychotic melancholic patients or in younger depressed patients; the actual cortisol concentration in 4 PM postdexamethasone blood samples may be significantly higher in psychotic and elderly depressed patients as well. The percentage of abnormal results on the DST is often reported to be lower than 50 percent in outpatients, perhaps 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 homogeneous, group of disorders than melancholia per se.

The DST abnormality appears to be stable over the course of a depressive episode and often remits 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 DST results with treatment precedes the clinical recovery; some have suggested that an incomplete normalization of the DST, irrespective of clinical symptoms, indicates 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 a higher likelihood of poor outcome. 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. A recent meta-analysis of the literature on the DST as a predictor of clinical course in depression concluded that baseline DST status does not predict response to treatment, with the exception that baseline nonsuppression predicts a poor placebo response; however, persistent nonsuppression after treatment was found to be a strong predictor of poor outcome.

The issue of the specificity of the DST for depression is an important one; in large measure it determines the test's clinical utility. The rate of false-positive results on the DST in normal subjects has varied from 4 percent to over 10 percent in different reports. One study suggested that the variability in those reports may have been due to an unrecognized history of mood disorders in the subjects or their relatives. In patients and normal subjects, variations in plasma dexamethasone levels after a fixed oral dexamethasone dose may contribute to some inconsistency in the DST data. Depressed patients may have lower dexamethasone levels than controls, but that difference alone does not appear able to explain the DST abnormality in depression. Differences in laboratory assay techniques and accuracy may also account for some of the reported variability in the DST data. Compliance with taking the dexamethasone is an obvious but sometimes overlooked potential confound. In addition, a number of medical disorders and pharmacological agents can produce false-positive or false-negative results. Weight loss per se, often an accompaniment of major depressive disorder, may also cause an abnormal DST result.

The literature on psychiatric conditions other than depressions that may be associated with an abnormal DST is considerable. The DST may be abnormal in some patients with panic disorder and obsessive-compulsive disorder, especially in severe cases in which secondary depression is suspected. Patients with anorexia nervosa and bulimia may also have abnormal DST results, even in the absence of major weight change. An abnormal DST is observed in many patients with depressionlike states after strokes, and also in persons withdrawing from alcohol. Although a number of investigators have found normal results on the DST in schizophrenic patients, the literature contains a few reports of a significant percentage of abnormalities on the DST in that group. High rates of DST nonsuppression have also been observed in manic patients.

As may be expected from the conflicting published reports, the possible clinical utility of the DST has attracted considerable controversy. Known factors that can produce a false-positive DST are expanding. Some investigators have suggested that postdexamethasone plasma cortisol levels may be of greater value than the mere qualitative assessment of the test as normal or abnormal. There is a reasonable consensus of opinion that the DST has little value as a diagnostic screening test for depression. But many investigators suggest that it may be helpful in difficult clinical situations (for example, in differentiating psychotic depression from schizophrenia). The ability of the DST to predict treatment response is limited. However, some investigators have taken the finding that an abnormal DST predicts a poor placebo response to suggest that a truly abnormal DST in a depressed patient may indicate the need for pharmacological treatment.

Other HPA axis abnormalities Over the past 10 years, abnormalities at a number of levels of the HPA axis have been identified in depressed patients. A number of studies have found that depressed patients have a greater output of cortisol in response to administration of synthetic ACTH than do controls. Moreover, the volume of the adrenal gland is increased in depressed patients compared with controls, suggesting that hyperplasia of the adrenal cortex may be responsible for the exaggerated response to ACTH. Another challenge strategy involved stimulation of the HPA axis by CRH. Studies have shown quite consistently that compared to healthy control subjects, depressed patients have a blunted output of ACTH in response to exogenous CRH (despite an apparent increased volume of the pituitary in these patients). An important finding, and one that has been replicated in independent samples, is that patients with major depressive disorder have increased levels of CRH in the CSF. This finding suggests that the blunted response to administered CRH may be due to down-regulation of pituitary CRH receptors. It has been proposed that the fundamental HPA axis abnormality in depression is hypersecretion of CRH; this putative defect is able to explain the abnormalities observed at lower levels of the axis. Hypersecretion of CRH itself could be due to a number of other abnormalities, including a defect in response to cortisol feedback at the level of the limbic system; abnormal feedback responses to administered cortisol have in fact been observed recently in depressed patients. CRH hypersecretion could also be caused by and could influence abnormalities in monoaminergic and other neuromodulatory systems that regulate CRH.

The relationship of HPA axis abnormalities to other biological variables is an important area for current and future research. Some reports have described a subgroup of patients with severe unipolar depressions who have increased catecholamine output (as reflected in very high levels of urinary MHPG) and evidence of high HPA axis activity (documented by elevated UFC levels or an abnormal DST). As noted earlier, the subgroup of depressed patients with high levels of urinary MHPG (subtype III) may have high norepinephrine output because of increased CRH activity in some cases. Investigators have also observed an association of increased platelet MAO activity with HPA axis hyperactivity, as detected by the DST, in some depressed patients. As with much of the data on the

HPA axis, further study is needed to clarify the meaning of this association.

HYPOTHALAMIC-PITUITARY-THYROID 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 (T_3) (Cytomel) potentiated the antidepressant effects of tricyclics, a finding that has recently been confirmed in a well-controlled study. In recent years, a number of subtle changes in the thyroid axis have been detected in patients with mood disorders.

The HPT axis, like the HPA axis, is a complex and highly integrated network. The hypothalamic peptide TRH is carried to the anterior pituitary by the pituitary portal circulation. TRH stimulates the release of the pituitary hormone thyrotropin (TSH), which regulates the production of the thyroid hormones L-thyroxine (T_4) and L-triiodothyronine (T_3). The thyroid hormones exert a feedback control over the axis.

Symptoms of depression have long been known to occur in patients with frank hyperthyroidism or hypothyroidism; the psychiatric symptoms generally revert with normalization of the thyroid status. Many psychiatric patients may exhibit transient changes in thyroid function test results at the time of hospitalization. These abnormalities, which generally revert to normal within a matter of weeks, may simply reflect the stress of acute illness. Some (but not all) recent studies have found that as a group, depressed patients have significantly lower TSH and higher free T_4 values than controls; some studies also suggest that response to antidepressant medication may be associated with a decrease in free T_4 level.

Some individual depressed patients, especially those with bipolar disorder, may exhibit persistent mild, or subclinical, hypothyroidism, detected by an elevated TSH value, an elevated TSH response to injected TRH, or the presence of antimicrosomal thyroid or antithyroglobulin antibodies. The relationship of these subclinical thyroid abnormalities to the effects of thyroid hormone augmentation of antidepressant medication is not clear, although a recent report suggests that depressed patients with subclinical hypothyroidism do benefit from the addition of thyroid hormone to their antidepressant regimen. Frank or subclinical hypothyroidism has been well documented in patients with rapid-cycling bipolar disorders. Interestingly, most patients with rapid-cycling disorders appear to benefit from hypermetabolic doses of thyroid hormone, regardless of whether the patient actually has subclinical hypothyroidism. The adjunctive benefit gained from the use of thyroid hormone in patients with affective disorder may derive, in part, from the thyroid modulation of adrenergic receptors.

TRH stimulation test The TRH stimulation test, a standard endocrine procedure, has been used to probe the HPT axis in patients with mood disorders but apparently normal thyroid functioning. In medicine, the test is used mainly for the evaluation of subtle dysfunction in the HPT axis. Often helpful in pinpointing the source of the dysfunction, it is considered to be a safe clinical procedure. The TRH test has become a useful research tool in psychiatry, one that may have clinical applications as well. Using the test, many investigators have consistently reported a decreased or blunted TSH response to TRH in depressed patients.

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 blood sample for TSH is drawn. 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 ΔTSH, or the highest TSH value after the TRH infusion minus the TSH value before TRH infusion. Because in depression the TSH values are likely to be low, the laboratory assay (generally a radioimmunoassay) must be sensitive to low levels.

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. One group of investigators performed TRH stimulation tests at 8 AM and 11 PM the same day in patients with major depression and in healthy control subjects. The difference between ΔTSH values at the two time points (11 PM minus 8 AM) defined as ΔΔTSH, was significantly lower in the patients. Setting the criterion for ΔΔTSH blunting at less than 3 mU/L, the test had a diagnostic sensitivity of 89 percent and specificity of 95 percent. Some groups have found that those patients with a blunted TSH response to TRH also have a blunted prolactin response or an abnormal GH response, but other groups have not had the same results. The possibility of differences in the blunting of the TSH response to TRH in bipolar versus unipolar depressions has been raised but not resolved in the literature.

Several factors are known to cause blunting in normal persons. Most important for the use of the test in psychiatry are increasing age and male sex. Many of the studies reported in depressed patients are hard to interpret because of lack of adequate controls. Other factors that may be related to blunting 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 suggested that the blunted TRH test in patients with depressive disorders might be an epiphenomenon related to an elevated plasma cortisol level. A number of recent studies, however, have separated these two factors. At times, TRH blunting and an abnormal DST occur in the same depressed patient. However, some patients exhibit only one abnormality, while others may have neither.

The possible diagnostic significance of TSH blunting has been a subject of some debate. Some 25 to 70 percent of patients variously described as having endogenous depression, primary depression, or major depression have a blunted TSH response to TRH. In two separate studies patients with TSH blunting were found not to be within particular familial subtypes of depression. Only a few studies have reported specifically on the TSH response to TRH in neurotic or minor depressions; in these studies the TSH response was normal, although one recent study found a 50 percent rate of TSH blunting in patients with subaffective dysthymic disorder. The TRH stimulation test has been normal in groups of patients with secondary depressions, schizophrenia, and acute paranoid reactions. Normal TSH responses, but with delayed time course, have been reported in patients with 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.

Thus, a blunted TSH response to TRH is not specific for

endogenous depression. Some have suggested, however, that with the proper exclusion criteria, it may be useful in the differential diagnosis of dysphoric states. Others do not agree. The recent findings of abnormalities in the diurnal variation of the TSH response to TRH suggest that this procedure may be more specific, but replication of these results will be important.

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 symptoms. 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. The possibility that TSH blunting may be a partial trait marker has stimulated studies of nondepressed relatives of TSH-blunted, depressed patients.

Some investigators have studied the prognostic value of the TRH test. One group reported that a blunted TSH response may predict a more favorable response to antidepressant drugs. Another group followed a cohort of clinically recovered depressed patients to determine relapse rates based on a ΔΔTSH index, defined as ΔTSH on a TRH stimulation test subsequent to a favorable treatment response minus ΔTSH on a TRH stimulation test performed before treatment began. In their studies, a ΔΔTSH above 2 mU/L was associated with no relapse within six months in 93 percent of cases, whereas a value of 2 mU/L or lower predicted a relapse within six months in 83 percent of cases. In all cases no maintenance treatment was continued after the clinical response. These investigators suggested that the ΔΔTSH index might be helpful in determining when to stop treatment. Other studies have confirmed the value of ΔΔTSH as a predictor of relapse, but it has not been clear that antidepressant therapy would prevent it.

A number of investigators have reported on the relationship of TRH test blunting to other biological measurements in depressed patients, but clear-cut, replicated findings have not yet emerged. Studies such as these, combining multiple biological tests, are likely to become increasingly common.

It is not known what relationship the TRH test blunting has to the augmented TSH response to TRH that may be seen in depressed patients with subclinical hypothyroidism. Moreover, the pathophysiological significance of the TSH blunting in mood disorders is not clear. Hypersecretion of TRH could lead to down-regulation of pituitary TRH receptors and produce TSH blunting. This possibility is supported by one report in the literature of elevated TRH in the CSF of depressed patients; however, a more recent study failed to replicate this finding.

HYPOTHALAMIC-PITUITARY-GROWTH HORMONE AXIS

The third endocrine system studied in patients with mood disorders is the HPGH axis. Investigators have looked at levels of GH and somatostatin (GHRIF), as well as the GH response to various stimuli, such as insulin hypoglycemia, L-dopa, 5-hydroxytryptophan, apomorphine, *d*-amphetamine, clonidine, growth hormone-releasing hormone (GHRH), and TRH. The findings in patients with mood disorders have been, in general, confusing; the HPGH axis is very complex.

GH 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. Adrenergic, serotonergic, cholinergic, and opioidergic inputs modify the production of hypothalamic GHRH and GHRIF, but the relationship of these factors to the pulsatile secretion is unclear.

Basal GH levels in depressed patients are generally reported to be grossly normal, despite the apparent stress of the illness. However, a reduction in mean GH levels (when measured every 15 minutes over 24 hours) has been observed. This overall reduction appears due to a decrease in GH secretion during sleep. An intermittent increase in daytime release of GH in depressed patients has also been noted.

Although a number of lines of evidence suggest that GH regulation may be abnormal in patients with depression, the picture is far from clear. Sleep-associated GH release may be low, and daytime GH secretion in depressed patients may be intermittently elevated. A number of studies have found that CSF levels of somatostatin (GHRIF) are decreased in depressed patients, but one study has not confirmed this finding. In addition, although some challenge tests of the GH system have substantiated the suspicion of abnormalities in depressed patients, others have not.

One challenge test, involving stimulation of the GH system with clonidine, has been reported fairly consistently to be abnormal in depression, although there have been recent negative findings. In this test, which measures the responsiveness of postsynaptic α_2-adrenergic receptors, depressed patients have a decreased GH response compared to controls. There have been suggestions that the abnormality persists after treatment and thus may represent a trait marker of depression or perhaps a severe form of depression. Another recently studied challenge test (measuring the GH response to desipramine, which also measures α_2-receptor sensitivity) has also been reported to show a decreased GH response among depressed patients.

Results from most other challenge tests of the GH system have been conflicting. As noted above, stimulation by L-dopa (Larodopa, Dopar) has been used as a measure of GH response. An early report suggested that depressed patients had a lower GH response to L-dopa; however, in a subsequent study that controlled for age, sex, and menopausal status, the diminished GH response to L-dopa disappeared.

Similarly, the use of amphetamine as a probe in patients with mood disorders has produced data the interpretation of which has changed in recent years. An early study reported that GH release after IV amphetamine administration was lower in patients with endogenous depression and higher in those with reactive depression as compared with normal controls. A subsequent report, however, suggested that age or estrogen status greatly influenced the amphetamine effect on GH. A restudy of GH release after amphetamine employing adequate control groups did not confirm the original findings.

There has been an interesting series of reports about abnormal positive GH responses to TRH in depressed patients. TRH normally causes the release of TSH and prolactin only. According to three separate groups, GH increases can be detected in approximately 50 percent of patients with either unipolar or bipolar depressions but in no patients with minor depression. The abnormality remits with clinical recovery. However, at least three other groups have not found an abnormal GH response to TRH in depressed patients. It is unclear why the findings are inconsistent. Further studies are required.

The availability of GHRH in recent years has allowed this peptide to be used in a challenge test with depressed patients. Again, the data are discordant. Some studies noted a blunted GH response to GHRH, others did not. Differences in methodology and in the form of synthetic GHRH used may explain

the differing results. Further investigations with the procedure are needed.

A number of investigators have noted a reduced GH response to insulin administration in some depressed patients. It may be more dramatic in psychotic depression and, in some cases may persist after clinical recovery. One report noted the GH reduction to be more pronounced in bipolar than in unipolar depressions; another report found just the opposite. One recent study, which controlled for adequacy of the hypoglycemic response to insulin, reported no evidence of an abnormal GH response, but a second investigation, which also assured an adequate hypoglycemic response, did note blunted GH secretion. Correcting for the hypoglycemic response to insulin is essential since some investigators have noted that unipolar depressed patients have a blunted hypoglycemic response to insulin. This latter effect, too, may be associated with more severe depressions.

The HPGH axis may provide intriguing clues to the pathophysiology of depressions but requires more intensive study. It must also be recognized that putative abnormalities in the HPGH system may be exceedingly difficult to interpret because of the complexity of the HPGH axis and its relationship with other neuroendocrine and neurotransmitter systems.

MELATONIN Melatonin, a hormone derived from the pineal gland, is synthesized from serotonin under the regulatory control of norepinephrine. Although the function of melatonin in humans is poorly understood, investigators have utilized it in the study of psychiatric disorders. For example, many, but not all, recent studies have suggested a relationship between light-induced changes in melatonin secretion and depressive symptoms. There has also been interest in nocturnal melatonin levels based in part on the fact that nocturnal synthesis and secretion of melatonin are controlled primarily by noradrenergic input to the pineal gland. A number of investigators have reported decreased nocturnal melatonin levels in depression. However, the only two studies that matched depressed patients and control subjects for age, sex, and menstrual status, variables known to affect melatonin secretion, failed to find significant differences in nocturnal melatonin concentrations between patients and controls; in fact, both studies showed trends toward significant increases in melatonin among the patients. There is a need for additional, well-controlled research on melatonin in depression; longitudinal studies of patients in different clinical states are particularly important.

OTHER BIOCHEMICAL ASPECTS OF MOOD DISORDERS

NEUROPEPTIDES In the past 20 years dozens of neuropeptides have been isolated and sequenced. The study of their multiple and complex actions throughout the nervous system has become a major thrust of neuroscience research. Possible relations between neuropeptides and psychiatric disorders have also been examined. Studies with the peptides CRH and TRH have added important information to the understanding of neuroendocrine axes in patients with mood disorders. Many other neuropeptides, including β-endorphin, β-lipotropin, somatostatin, arginine vasopressin, cholecystokinin, substance P, bombesin, vasoactive intestinal peptide, δ-sleep-inducing peptide, calcitonin, neuropeptide Y, and diazepam-binding inhibitor, have also been studied in patients with mood disorders. Unfortunately, the information reported for these neuropeptides is conflicting and, for some, quite sparse. Those that have been studied the most are β-endorphin, somatostatin, and arginine vasopressin.

The well-known effects of administered opioids and the discovery of endogenous opioid peptides led to questions about the role of the opioid peptides in mood disorders. Some have suggested that administered opioids might have antidepressant effects, or that opioid antagonists might worsen depression and lessen mania. A number of studies have failed to provide evidence supporting these ideas; there is, however, one study suggesting that a high dose of the opioid antagonist naloxone (Narcan) may exacerbate depression.

ACTH and β-endorphin are cleavage products of a common precursor, pro-opiomelanocortin (POMC), and this posttranslational processing occurs under the regulation of CRH. For that reason, changes in β-endorphin have been studied to provide further information about the integrity of the HPA axis in depressed patients. Some investigators have reported elevated plasma levels of β-endorphin in depressed patients, although negative findings have also been reported. There may be a negative correlation between β-endorphin levels and symptom severity. Plasma levels of β-endorphin have also been used as an index of pituitary response to dexamethasone. High rates of failure to suppress β-endorphin (after dexamethasone) have been found in depressed patients, and some depressed patients who suppress cortisol fail to suppress β-endorphin. Studies of CSF β-endorphin or total opioid binding in depressed patients have not shown the same changes seen with plasma measures.

As noted above, somatostatin (GHRIF) has been studied in patients with mood disorders as an indicator of GH axis regulation. Somatostatin, however, is a neuromodulator with complex actions impinging on many other neurotransmitter systems. Because of its widespread actions, somatostatin has been thought to play a role in the behavioral, physiological, and endocrine changes in patients with mood disorders. At least four separate studies have shown decreases in CSF somatostatin levels in patients with depression, but one study has reported no decrease. Any relationship, however, will be complex, as somatostatin levels are also related to sleep, which is frequently disturbed in depressed patients.

Arginine vasopressin (AVP) is known to be widely distributed throughout the CNS, where it functions as a neuromodulator and produces complex behavioral effects. Preclinical studies have suggested that the actions of AVP may be related to memory, rapid-eye-movement sleep, biological rhythms, and neuroendocrine function, all thought to be altered in patients with mood disorders. In clinical research, one study found CSF AVP levels to be significantly lower in depressed patients than in controls and to be significantly higher in manic than in depressed patients. In another study, when the vasopressin analogue 1-desamino-8-D-arginine vasopressin (desmopressin, DDAVP [Adiuretin]) was given to four depressed patients, their cognitive function improved without a change in mood. Because ACTH release by the pituitary is regulated in part by AVP, the ACTH response to AVP administration has been examined in depressed patients. In contrast to the blunted ACTH response to administration of CRH found in depressed patients, AVP administration does not appear to produce a decreased ACTH response in depressed patients compared with controls; there is even a suggestion that depressed patients may have an exaggerated ACTH response to a low dose of AVP.

PSYCHOIMMUNOLOGY Although some studies suggest that bereavement and depression can interfere with immuno-

logical competence, the findings in this area of research have been diverse and often inconsistent. Studies of bereaved men and women have reported reduced in vitro lymphocyte response to mitogen stimulation, with normal levels of circulating immunoglobulins and normal responses on delayed hypersensitivity skin tests; the reduced lymphocyte response is most dramatic in bereaved patients with depressive symptoms. A recent meta-analysis of methodologically sound studies addressing cellular immunity in depression found that the immune abnormalities reliably associated with depression were (1) decreased proliferative response of lymphocytes to mitogen stimulation, (2) decreased natural killer cell activity, and (3) abnormalities of different white blood cell lines. The magnitude of these immune system abnormalities correlated with the intensity of depressed mood. However, one review cautioned that methodological concerns limit the interpretation and generalizability of much of the available data on the immune system in depression, and another review, noting the high incidence of failure to replicate findings, concluded that specific or reproducible abnormalities of the immune system in depression have not been demonstrated.

A potential explanation for some of the diverse findings may involve high catecholamine output and the increased production of prostaglandins, each of which has been observed separately in studies of depressed patients. Catecholamines, acting through β-adrenergic receptors, are known to suppress the activity of human natural killer cells. Prostaglandins, functioning through a complex interaction between second messenger systems, may inhibit in vitro mitogen-induced lymphocyte proliferation. Because recent animal work suggests that prostaglandin production is increased by catecholamines through a nonreceptor-mediated mechanism, the diminished immunological competence reported in depressed patients may be a result of the dysregulation of the catecholaminergic system.

GABA METABOLISM AND PHYSIOLOGY Recent studies have found that plasma levels of GABA, which reflect brain GABA activity, may be decreased in certain patients with unipolar or bipolar depressions or during manic episodes. In the patients with unipolar depression and low GABA levels, the GABA level did not appear to correlate with severity or duration of illness, and the low plasma levels persisted after remission of the depressive illness. This finding raises the possibility that, in some patients, plasma GABA may be a trait marker of depression.

INTRACELLULAR CALCIUM Several recent studies have suggested that abnormalities of intracellular calcium are associated with mood disorders. Basal concentrations of intracellular free calcium ion appear to be elevated in platelets and lymphocytes obtained from patients with bipolar disorders during either manic or depressed episodes; in contrast, patients with unipolar depression appear to have normal basal levels of calcium in these cells.

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

The mood disorders include a heterogeneous group of conditions. Clinical subtyping of these disorders has been only partially successful in identifying homogeneous categories; even within categories (such as major depressive disorder) the natural history of the disorder may vary, as may the response to treatment. It is also generally recognized that the clinical categories do not necessarily represent distinct biologically homogeneous entities. For these reasons, studies have examined various biochemical characteristics that might serve as independent variables for classifying subtypes of mood disorders.

Studies of the biogenic amines have revealed important clues about the pathophysiology underlying the heterogeneity of mood disorders. For almost 30 years the catecholamine hypothesis proved to have heuristic value. It gave both investigators and clinicians a frame of reference for understanding much of the available data on mood disorders, and it stimulated new research on their biochemistry.

The field continues to evolve, and much new information is being accumulated, not all of which can be fitted into any one theoretical framework. Intriguing clues across the biological variables have begun to appear. The process of norepinephrine-induced heterologous desensitization, if confirmed, may provide a useful link among some of those variables. But that work, like much of the new research, is still preliminary. Perhaps the best synthesis that can be currently offered should emphasize two facts: The mood disorders are most likely a group of interrelated neuroendocrinometabolic disorders, and biochemical procedures will be required to subdivide and classify them.

The development of a biochemical classification of depressive disorders will require, in part, empirically derived clinical laboratory tests that reflect one or another aspect of the pathophysiology of these disorders. It seems highly unlikely, however, that there will be a truly comprehensive understanding of the etiology and pathophysiology of the depressive disorders until a parallel description of the functional neurochemistry and neurophysiology of the normal human brain becomes available. Eric Kandel's pathfinding studies using animal models to explore specific forms of behavior at the cellular and molecular levels demonstrated the feasibility of such an undertaking but also underscored how far away is the attainment of that goal. Thus, in the foreseeable future, psychiatric practice may be guided by the use of specialized clinical tests that may not be meaningfully integrated into the theory of psychiatry for many years. In this regard, however, psychiatrists are in a position quite similar to that of their colleagues in other medical specialties.

It may be useful to compare the pneumonias and the depressions. Both disorders are diagnosed on the basis of clinical data, and both are treated more effectively using information gleaned from clinical tests. In the case of pneumonias, the physician makes a diagnosis on the basis of the history and physical examination (including a chest X-ray). After the diagnosis is made, sputum cultures are 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 the clinical history and findings on physical and mental status examinations. 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 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

Monoamine neurotransmitters are discussed in Section 1.3, and the contributions of the neural sciences in general are the focus of the other sections of Chapter 1. Biological therapies are covered in Chapter 32.

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16.4 MOOD DISORDERS: GENETIC ASPECTS

KATHLEEN RIES MERIKANGAS, Ph.D.
DAVID J. KUPFER, M.D.

INTRODUCTION

Rapid developments in molecular biology have introduced a new era in human genetics. Although only a decade ago linkage depended on inferences about the underlying genetic alleles from phenotypic expression of known markers, advances in the identification of polymorphic deoxyribonucleic acid (DNA) markers and the methods for processing and sequencing the DNA have enhanced dramatically the ability to detect linkage between those markers and diseases for which no aberrant gene product has been identified. Family pedigrees may be examined to determine whether a particular disease or trait is associated with a specific DNA marker (linkage). Since the exciting discovery of a linked marker for Huntington's disease, studies of numerous other diseases have followed, and the primary gene defect has now been discovered for Duchenne's muscular dystrophy and cystic fibrosis. Those dramatic discoveries have led to a new focus on the role of genes in the etiology of major psychiatric illness.

In a field plagued by complexity of expression and lack of valid definitions of discrete disorders, coupled with the little progress in uncovering the cause of psychiatric disorders, the application of molecular biological approaches has provided a renewed opportunity for researchers to identify markers for psychiatric disorders. Such markers may serve as vulnerability or disease indicators with which to circumvent the exclusive reliance on clinical signs and symptoms to diagnose psychiatric illness. However, the initial enthusiasm engendered by the potential yield of these methods has diminished after five years of inconsistent and disappointing results involving labor-intensive and costly research.

The major psychiatric disorders consist of disorders for which the validity of definitions has yet to be established, the cause is unknown, and the pathway from genotype to the phenotype is complex and probably heterogeneous. The new field of genetic epidemiology, with an integration of knowledge from clinical psychiatry, neurobiology, molecular biology, immunology, and endocrinology, provides hope of unraveling some of the complexity that continues to obscure the etiology and pathogenesis of the psychiatric conditions. The disorders are among the most prevalent and distressing of all chronic human diseases. Specification of the role of genetic factors for a disease may also lead to the identification of critical environments for its expression. In fact, knowledge of the role of genetic factors may lead to prevention and amelioration of the diseases by purely environmental methods. Even without accomplishing the ultimate aim of specification of causation, a considerable degree of optimism is warranted that the current generation of genetic epidemiology studies may yield information that will enable prevention and intervention efforts to minimize the effects of the disorders.

Although caution is warranted in the investigation of the cause of complex disorders, that does not imply that discovery of the role of genes is a phenomenon in the distant future. Recent developments in the understanding of human cancers, including retinoblastoma and an early-onset form of breast cancer, demonstrate the importance of inheritance of genetic factors which, in the presence of particular environmental factors, lead to the development of disease.

BACKGROUND

HUMAN GENETICS Human genetics, the scientific study of heredity, began in the early 1900s with the integration of mendelian theory and the basic principles of population genetics. The major subdivisions of human genetics that have evolved include biochemical genetics, population genetics, cytogenetics, molecular genetics, and immunogenetics. Genetic epidemiology is primarily derived from the division of population genetics.

Each normal human being has 23 pairs of chromosomes, the cellular components that are bearers of heredity, which are found exclusively in the nucleus of all living cells. Humans have 22 pairs of autosomes and one pair of sex chromosomes, with one member of each pair deriving, respectively, from maternal and paternal lines. Chromosomes have two components: DNA, and a class of small, positively charged proteins called histones. DNA is comprised of two complementary strands of nucleotides. There are four nucleotides—adenine and thymine, guanine and cytosine—each of which pairs exclusively with only one of the other three. Various combinations of three of the nucleotides code for amino acids, which are then joined sequentially to form specific proteins. The two intermediate steps in the process involve (1) in the nucleus, transcription of one of the DNA strands to its complement or messenger ribonucleic acid (mRNA) (which is identical to DNA except that the nucleotide uracil replaces thymine, and the sugar is ribose rather than deoxyribose), and (2) translation of the mRNA into a sequence of amino acids with the assistance of transfer-RNA (t-RNA) on the ribosomes in the cytoplasm of the cell.

All sequences of DNA are not active coding regions. Within genes, active coding sequences, or exons, are interspersed among introns, the noncoding sequences and intervening sequences. Enhancers, promoters, and control sequences are located at one end of a gene. Control of gene activity (protein synthesis) is a complex process that can occur at several different levels. The signals that turn genes on and off are mediated by or generated within the cytoplasm of the cell by the presence of activating or inhibiting molecules, such as hormones.

However, even after a protein has been manufactured, there still remains a complex pathway to its final expression in the phenotype, which may depend on the presence or absence of a variety of other genetic and environmental factors. For example, the disease phenylketonuria (a homozygous recessive condition resulting from a mutation in the gene coding for the enzyme phenylalanine hydroxylase, which converts the amino acid phenylalamine to tyrosine) results in permanent brain damage only if the vulnerable individual is exposed to typical levels of phenylalanine in the diet.

One-to-one correspondence between genotype and disease is often absent, even for traits that are produced by known genetic loci. Examples of this phenomenon include the following: epistasis, the interaction between distinct genes; variable expressivity, variation in the effects of a particular gene; genotype-environment interaction, genotypes that produce different phenotypes depending on the environment in which they are expressed; and reduced penetrance, the situation in which persons with a relevant genotype express a phenotype mildly *(formes fruste)* or not at all. Conversely, a single gene can have multiple effects (pleitropy). Because the complexity of the genotype is expected to exceed that of the phenotype, which only has a limited repertoire of expression, some investigators recommend that studies should begin at a phenotypic level and proceed backward toward the level of the genotype. Alternatively, other scientists argue that genetic heterogeneity, together with the other factors that are related to a lack of one-to-one correspondence between the genotype and the phenotype, strongly limit the ability of phenotypic studies to identify the underlying gene mechanisms. Instead, they suggest that molecular genetics studies of single large pedigrees are more likely to yield information on the genetic factors involved in a complex disorder.

GENETIC EPIDEMIOLOGY Although there have been major advances in the fields of epidemiology and human genetics, particularly in biostatistical methods (spurred by the integration of molecular biology and population genetics), there has been little communication between researchers in the fields of genetics and epidemiology. Although the goal of epidemiology is to study the interaction between host, agent, and environment, epidemiologists have tended to neglect "host" characteristics other than demographics. Similarly, geneticists have often neglected to consider the environment as a potential etiological agent, either randomizing or controlling for it in their analyses. Geneticists consider the environment as "noise" and heredity as "signal," whereas epidemiologists do the opposite.

Despite their history of independence, the two fields share much common ground. Both are interested in determining the causes of complex human disorders and predicting familial recurrence risks for such disorders. The advent of the new field of genetic epidemiology, defined as a science that deals with the cause, distribution, and control of disease in groups of relatives, and with inherited (biological or cultural) causes of disease in populations, has served to bridge the gap between the two fields. Newton Morton notes that the "synthesis of genetics and epidemiology is necessary before diseases of complex etiology can be understood and ultimately controlled." Hogben in 1933, quoted by Harris in 1977, has noted that in metaphoric terms, stating: "... our genes cannot make bricks without straw. The individual differences which men and women display are partly due to the fact that they receive different genes from their parents and partly due to the fact that the same genes live in different houses. . . ."

Genetic epidemiology is a relatively new discipline that has emerged from an integration of methods from the fields of population and clinical genetics, and chronic disease epidemiology. Until relatively recently, studies currently within the domain of genetic epidemiology were conducted within the realm of clinical genetics or behavior genetics. However, with the increasing awareness of the importance of simultaneous consideration of the relationship between the background population characteristics and the role of environmental factors in gaining understanding of the pathophysiology of disease, the discipline of epidemiology has become a critical component of genetic studies. During the past 10 years, the discipline of genetic epidemiology has grown rapidly, as exemplified by the introduction of the journal *Genetic Epidemiology* and the publication of several new textbooks describing a wide variety of applications and methods in the field. The application of the techniques of the new field of genetic epidemiology, which is without either environmentalist or hereditarian bias, should result in substantial contributions to the understanding of psychiatric disorders.

The most common misconception regarding the role of genetic factors in the manifestation of a particular trait or disease is that the term "genetic" implies determinism by innate factors with a subsequently unalterable course. Nothing has impeded progress in knowledge of the development of human traits and disorders more than the nature versus nurture controversy. The concept was originally introduced by Francis Galton in 1894 as nature and nurture. The majority of known genetic traits are not totally independent from the environment in which they are expressed. An illustrative example of gene-environment interaction is glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder caused by a mutation on the long arm of the X chromosome. The expression of the disorder manifests as hemolytic anemia only when the susceptible individual is exposed to certain drugs or to fava beans. Genes may also be involved in the response or resistance to purely environmental agents such as diet, stress, exercise, drugs, and nutritional deficiencies, through the activity of immunogenetic factors of the major histocompatibility complex.

Not only is the expression of genes modified by the environment, but there is now substantial evidence that numerous environmental factors may actually alter the genotype. For example, environmental agents may induce chromosomal mutations that lead to carcinoma, such as the role of Epstein-Barr virus in Burkitt's lymphoma, or tobacco smoking in small cell carcinoma of the lung.

Design and analysis of genetic epidemiological studies Descriptive epidemiological studies are important in specifying the rates and distribution of disorders in the general population. The data can be applied to identify biases that may exist in treated populations and case registries from which persons who serve as probands in family, twin, and adoption studies are selected. Such persons often constitute the tip of the iceberg of the disease and are not representative of the general population of similarly affected persons with respect to demographic, social, or clinical characteristics.

The traditional case-control study, an epidemiological study design, has been employed to study familial aggregation of disease in two ways: one in which the frequency of a positive family history among the cases is compared with that among the controls, and one in which the retrospectively assessed course of relatives of the cases is compared with that of the controls (retrospective cohort study).

After familial transmission of a trait has been established, the immediate goal of genetic epidemiological studies is to identify the relative degree of phenotypic variance that can be attributed

to genetic factors and to transmissible and nontransmissible environmental factors. The ultimate purpose of such studies is to identify the specific agents that play an etiological or contributing role to the development of the trait.

The two chief study paradigms for studying gene-environment interactions involve holding either the genetic background or the environment constant and evaluating systematic changes in the other. Examples of studies that hold the genetic background constant while observing differential environmental exposures include studies of discordant twins; migrant population studies; relatives exposed to a particular agent, such as a virus; twins reared separately; or the family set design, in which comparisons are made among families of similar structure living in distinct environments. Examples of paradigms in which the environment is held constant and genetic factors are allowed to vary include monozygotic twins of affected individuals compared with dizygotic twins and nontwin siblings; offspring of consanguineous matings compared with offspring of nonconsanguineous matings; half-siblings compared with full siblings living in the same home; and first-degree relatives of affected persons. In both types of studies, observations can be made regarding time-space clustering of disease, which can provide information regarding environmental agents, or a characteristic age of onset and course, which may provide information on genetic factors.

Application of the genetic-epidemiological approach has also yielded information on risk and etiological factors for a number of disorders such as diabetes, hyperlipidemia, and coronary heart disease. An exemplary study of monozygotic twins who were concordant for heart disease but discordant for cigarette smoking demonstrated that smoking was not a risk factor for coronary heart disease. However, the twin pairs were found to be discordant for lung disease, which was found to be strongly related to cigarette exposure.

The importance of the integration of epidemiological methods in genetic studies is underscored by the results of family, twin, and adoption studies of numerous complex human disorders which suggest the importance of both genetic and nongenetic contributions to their causation. Such an approach is illustrated by the identification of the causes of specific types of cancer, such as retinoblastoma, which results from an interaction between an inherited gene defect and an environmentally induced mutation of the second allele at that locus.

It is often difficult to distinguish between transmitted and genetic factors, because environmental factors are often confounded with genetic susceptibility to those factors. The effects of putative exogenous factors such as drugs, dietary factors, and physical factors such as stress, fever, and exercise, may be modified by immunogenetic factors or by genetic variation in enzymes, hormones, fatty acids, or neurochemicals. In addition, factors that may appear to be purely environmental may actually be a result of transmissible factors.

GENETICS OF MOOD DISORDERS: REVIEW OF EMPIRICAL EVIDENCE

EPIDEMIOLOGY OF MOOD DISORDERS The lifetime prevalence of bipolar disorder ranges from 0.6 to 0.9. The incidence rates of bipolar disorder range from 9 to 15.2 new cases per 100,000 population per year for men and 7.4 to 32 new cases per 100,000 per year for women. For major depressive disorder the lifetime prevalence is 2.0 to 12.0 for men and 5.0 to 26.0 for women. The aggregate incidence rates of major depressive disorder are 247 to 598 per 100,000 per year for women and 82 to 201 for men. The results derived from the Epidemiologic Catchment Area Study, a large epidemiological survey of psychiatric disorders in the United States, yielded rates within the above-cited ranges for both bipolar disorder and major depressive disorder.

The demographic distribution of bipolar disorder and depressive disorders exhibits several differences: The sex ratio favors women for depressive disorders, whereas there is a nearly equal distribution of men and women for bipolar disorder. A family history of depression is the most important risk factor for both mood disorders, and both generally begin in early adulthood, with bipolar disorder having an earlier age of onset than major depressive disorder.

METHODS AND STUDY DESIGNS IN GENETIC EPIDEMIOLOGY There are four types of evidence that genetic factors contribute to a disease of unknown cause: (1) significant aggregation of the illness within families; (2) a higher concordance among monozygotic twins than among dizygotic twins; (3) a higher incidence of the trait, irrespective of home environment, among biological offspring of affected persons than among biological offspring of unaffected persons (that is, positive adoption study); and (4) linkage of the illness with an identifiable allele at a marker locus.

The types of studies that have been conducted to assess the role of genetic factors in the etiology of illnesses include the following: (1) family studies, which assess the degree of aggregation of a trait among relatives of affected probands compared with expected rates from the general population; (2) twin studies, which compare concordance rates for monozygotic twins, who have identical genotypes, with those among dizygotic twins, who share an average of half of their genes in common; (3) adoption studies, which compare the degree of similarity between an adoptee and his or her biological parents, from whom he or she was separated, and between the adoptee and the adoptive parents. Those comparisons yield relative risks of the genetic and environmental factors and their interaction in producing a disease; and (4) association and linkage studies of genetic markers, which examine the relationships between a known genetic trait and disease status either across families or within pedigrees.

Specific analytical techniques that are applicable to each type of study include comparison of morbid risk or correlations among relatives of a proband with risk in the population-at-large; path analysis, which partitions the total variance of the pairwise correlations between different types of relatives into genetic, cultural, and random environmental components; computation of pair or proband concordance for monozygotic versus dizygotic twins; comparison of correlations of adoptees with their biological siblings or parents and with their adoptive siblings or parents; and the sibling pair and LOD (logarithm of the odds) score methods of linkage analysis (described later). After the involvement of a genetic component in a disease has been established, there are numerous analytical methods for the detection and identification of the role of major genes, such as segregation analysis, disease-marker association studies, and linkage analysis.

FAMILY STUDIES

Designs and methods Familial aggregation of a disease is generally the initial source of evidence suggesting the involvement of genetic factors in its causation. However, common environmental factors such as diet, infection, shared behavioral patterns, or stress may also lead to familial clustering of a dis-

ease. The major goal of family studies is to understand the magnitude and patterns of familial aggregation of a particular disease.

Although family studies cannot yield direct evidence for the involvement of genes in the causation of a disease, they are a rich source of evidence for examining the correspondence between the observed patterns of expression of a disease and the patterns predicted by specific modes of transmission. A second application of family studies is the investigation of the validity of diagnostic categories and their subtypes through inspection of the degree to which particular symptoms or symptom constellations breed true in families. Whereas the homogeneity of expression of disorders is the goal of the latter studies, information on heterogeneity of expression within families may also be employed to identify variable expressivity of transmitted disorders.

A major advantage of studying diseases within families is that the assumption of homotypy of the underlying factors eliminates the effects of heterogeneity that are present in comparisons made between families. However, all individuals within a particular sibship are not expected to share equal genetic risk because of independent segregation of genes. Nevertheless, if two members are affected, similar etiological factors can be assumed, and variable forms of expression can be identified.

The three major designs of family studies are as follows: (1) increased prevalence of a disease among relatives of an affected proband compared with disease occurrence in the population from which they were selected; (2) increased prevalence of a disease among the relatives of an affected proband compared with a comparable group of relatives of controls; and (3) patterns of disease expression that do not differ from the predictions of specific genetic models of disease transmission.

Family studies may be analyzed as either traditional case-control studies in which the family history is classified dichotomously according to the presence or absence of a disorder in at least one of the first-degree relatives of persons with the disease compared with those without the disease, or through the calculation of rates of the disorder among the first-degree relatives of probands compared with rates among controls. The advantage of the latter approach is that information on the full pedigree may be employed, whereas the former approach eliminates possible bias associated with the lack of independence of observations obtained within families.

Modes of familial transmission Table 16.4-1 summarizes the major models of disease transmission and the expected patterns of illness within pedigrees according to each model. Adequate fit of the models to the observed data does not provide positive evidence regarding the mode of transmission of a disorder. Rather, those models that do not provide an adequate fit to the data can be excluded as explanations of the mode of transmission of a particular disorder if the assumptions of the model are not violated.

The traditional single major locus mendelian models have rarely fit family data for the major psychiatric disorders (with the exception of some bipolar disorder pedigrees, described later). However, the models may still provide a good fit to subtypes of the psychiatric disorders. Despite the recent progress in the development of standardized diagnostic nomenclature, definitions of psychiatric disorders still suffer from a lack of established reliability and validity, thereby casting doubt on assignment of disease status in probands and their families. The lack of adequate models of disease transmission is one of the major obstacles to progress in linkage studies of those conditions. Furthermore, the probable genetic heterogeneity or different genetic factors resulting in similar phenotypic expression of the major psychiatric disorders also compromises current attempts to identify the role of genes in these conditions.

TABLE 16.4-1
Observed Patterns of Transmission for the Major Genetic Models

Model	Observed Patterns
Autosomal dominant	Every generation, no skipping Unilineal transmission Half of the relatives affected
Autosomal recessive	Horizontal transmission One fourth of siblings affected Equally affects men and women Consanguinity increased in parents
X-linked recessive	Men are affected to a greater extent than women Absence of male-to-male transmission Half the sons of female carriers are affected All daughters of affected men are carriers
X-linked dominant	Women are affected more than men Affected women transmit trait to half of their sons and half of their daughters Affected men transmit to all daughters, but not to sons
Multifactorial	One Gene (polygenic) and more than one nongenetic factor Risk among relatives increased according to severity of the proband disorder Bilineal transmission common Mean for offspring midway between parents and population values (continuous traits) Recurrence risk (dichotomous traits) or correlation (continuous traits) among relatives proportional to the degree of the genetic relationship
Mixed model: single major locus (SML) and multifactorial	Three distributions within a single skewed distribution

The multifactorial model of disease transmission, first proposed by Douglas Falconer, specifies that there are numerous genes and transmissible and nontransmissible cultural factors that are additively and independently (without epistasis) involved in producing a phenotype. There is assumed to be a continuous underlying distribution, or liability, which is defined as the propensity for expressing a disease. The total liability includes a genetic (transmitted) component and a nontransmitted component of the variance. The liability is assumed to be normally distributed, with mean = 0 and a variance = 1. The disorder becomes apparent after the accumulation of vulnerability factors surpass the threshold, or the point on the distribution beyond which the disorder becomes manifest.

The analytical technique that has been frequently applied to resolve the polygenic and cultural components under multifactorial transmission is path analysis. The basic parameters are paths, copaths, and correlations between pairs of relatives throughout an extended pedigree. Allowance is made for assortative mating, correlated environments between pairs of individuals, and unique environments of individuals. The observed and expected values of the correlations are compared and tested for statistical significance. Resolution of cultural and biological inheritance requires either extended familial relationships (monozygotic twins, half siblings), or the identification of a relevant index of inherited environment.

Methodological standards for family studies of psychiatric disorders Several large-scale family studies during the past decades have developed standard methods for conducting family studies of the major psychiatric disorders. The following design features are included: recruitment of a well-characterized homogeneous group of probands with a particular disorder; selection of a control group of persons who are comparable with the affected probands on all possible confounding factors except the disorder itself; systematic enumeration of all living and deceased relatives according to the degree of relationship to the probands and controls; use of structured diagnostic interviews with relatives using predetermined diagnostic criteria and reliable and valid diagnostic instruments; maintenance of blindness with respect to the diagnostic status of the proband in collecting diagnostic information from the relatives and formulating the final diagnostic estimates; collection of information regarding relatives unavailable for interview in a standardized format from as many informants as possible; inclusion of ancillary information to supplement interview and family history data; development of reliable procedures to integrate material from direct interviews, family history reports, and ancillary medical or psychiatric information in deriving the diagnostic assignment of the probands and relatives; and application of sophisticated statistical techniques to control for confounding variables and simultaneously adjust for length of observation of the relatives.

Empirical evidence: family studies For centuries, depression has been known to occur often in closely related family members. The tendency for melancholia to pass from parent to offspring was noted by Hippocrates in ancient Greece. Numerous family studies of manic depression conducted in Europe during the first half of the 20th century have shown that manic depression was familial. The first systematic family studies which separated bipolar and unipolar depression revealed that bipolar depression was familial, but that unipolar depression was not increased among the relatives of bipolar probands and the converse.

Although numerous family studies of both bipolar disorder and major depressive disorder have been conducted during the past 30 years it is remarkable that only four family studies of bipolar disorder and five studies of major depressive disorder meet the previously cited standards of family study methodology—including inclusion of control probands and relatives, application of standardized diagnostic criteria with structured diagnostic instruments, and blindness with respect to the diagnosis of the probands.

Table 16.4-2 summarizes the series of controlled family studies of probands with bipolar disorder. The results of the studies consistently reveal a significantly greater risk (range, 3.7 to 17.5 percent) of bipolar disorder among the relatives of bipolar probands compared with risk among the relatives of controls. The absolute rates of bipolar disorder among the relatives of bipolar probands are quite similar, ranging from 3.8 to 6.8 percent. The rates of major depressive disorder among the relatives of bipolar probands are also consistently elevated but of a much lower magnitude than those of bipolar disorder. In accordance with expectations derived from epidemiological studies, the rates of major depressive disorder are greater than those of bipolar disorder, with a range from 6.8 to 16.7 percent. There is an average twofold increase in the relative risk of major depressive disorder among the relatives of bipolar probands compared with risk in relatives of controls.

Investigations of the familial aggregation of mood disorders among the relatives of probands with major depressive disorder compared to controls are shown in Table 16.4-3. The magnitude of rates of bipolar disorder among the relatives of major depressive disorder probands is about half that of relatives of bipolar probands. Similarly, the relatives' risks, although significantly elevated in two of the studies, appear to be attributable to extremely low rates of bipolar disorder in the relatives of controls (0.2 percent, which is significantly less than expectation of bipolar disorder in the general population). Thus, the evidence for transmission of bipolar disorder among probands with major depressive disorder is weak and may be an artifact of differences in control samples.

In contrast, rates of major depressive disorder are significantly greater among the relatives of patients with the disorder compared with relatives of controls. There is an average twofold increase in the risk of major depressive disorder among the relatives of patients with that condition, thereby suggesting some degree of specificity of transmission of both bipolar disorder and major depressive disorder in families.

Factors associated with familial transmission of affective disorders The transmission of mood disorders may vary according to polarity, degree of relationship to the proband, age of onset of disorder in the proband, and the sex of the proband and of the relative. Many of the family studies cited have explored the relationship between the proband characteristics and those in their relatives.

RELATIONSHIP TO THE PROBAND Numerous studies have presented the rates of mood disorders among both the first- and second-degree relatives of mood disorder probands. According

TABLE 16.4-2
Controlled Family Studies of Bipolar Probands

Author and Year	Status	Number of Relatives	% Bipolar Disorder in Relatives	Relative Risk	% Major Depressive Disorder in Relatives	Relative Risk
Gershon et al 1975	Cases	341	3.8	17.5	6.8	9.7
	Controls	518	0.2		0.7	
Tsuang et al 1980	Cases	100	5.3	17.7	12.4	1.7
	Controls	160	0.3		7.5	
Winokur and Crowe 1983	Cases	196	1.5	5.0	12.8	1.8
	Controls	344	0.3		7.3	
Gershon et al 1982	Cases	401	4.6	—	14.0	2.4
	Controls	217	0		5.8	
Maier et al 1991	Cases	389	4.4	3.7	11.1	1.6
	Controls	419	1.2		6.9	

Data compiled from Taylor M A, Berenbaum S A, Jampala V C, Cloninger C R: Are schizophrenia and affective disorder related? Preliminary data from a family study. Am J Psychiatry *150:* 278, 1993; Maier W, Lichtermann D, Minges J, Hallmeyer J, Heun R, Benkert O, Levinson D F: Continuity and discontinuity of affective disorders and Schizophrenia. Results of a controlled family study. Arch Gen Psychiatry *150:* 871, 1993.

TABLE 16.4-3
Controlled Family Studies of Probands with Major Depressive Disorder

Author and Year	Status	Number of Relatives	% Bipolar Disorder in Relatives	Relative Risk	% Major Depressive Disorder	Relative Risk
Gershon et al 1975	Cases	96	2.1	10.5	11.5	18.9
	Controls	518	0.2		0.7	
Tsuang et al 1980	Cases	225	2.2	11.0	11.0	2.0
	Controls	160	0.2		4.8	
Gershon et al 1982	Cases	112	1.5	—	12.8	2.9
	Controls	217	—		5.8	
Weissman et al 1982	Cases	133	2.3	1.4	14.9	3.1
	Controls	82	1.6		5.6	
Winokur and Crowe 1983	Cases	305	1.0	3.3	11.2	1.5
	Controls	344	0.3		7.3	
Maier et al 1991	Cases	221	1.4	1.2	11.3	1.6
	Controls	419	1.2		6.9	

Data compiled from Taylor M A, Berenbaum S A, Jampala V C, Cloninger C R: Are schizophrenia and affective disorder related? Preliminary data from a family study. Am J Psychiatry *150:* 278, 1993; Maier W, Lichtermann D, Minges J, Hallmeyer J, Heun R, Benkert O, Levinson D F: Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. Arch Gen Psychiatry *150:* 871, 1993.

to expectations of traditional genetic models, risks to all classes of first-degree relatives should be equal for dominant traits, whereas siblings should have increased rates of disorders for recessive traits. The aggregate data for bipolar disorder reveal that the risk of bipolar disorder among parents and siblings are approximately equal for both bipolar and major depressive disorder. However, the offspring tend to have elevated rates of bipolar disorder and equal rates of major depressive disorder when compared with parents and siblings. In the absence of control data, it is difficult to interpret the latter finding. However, the elevation in the risk among offspring could result from comorbidity, recall bias, a cohort effect, or assortative mating in the parental generation.

Most genetic models predict a decrement in risk of disease according to the degree of relationship to the affected proband. Although a large number of studies have reported rates of mood disorder among both the first- and second-degree relatives, there is only a single controlled study in which the rates of mood disorders were compared between the first- and second-degree relatives and with controls. The results of that study revealed that the rates of bipolar disorder among first-degree relatives of bipolar probands were approximately twice those of second-degree relatives, which in turn were greater than those of controls. In contrast there was no elevation in the rates of either major depressive or bipolar disorder among the second-degree relatives of major depressive disorder probands, nor was there an increased rate of major depressive disorder among the second-degree relatives of bipolar probands.

AGE OF ONSET The effect of age of onset on the familial aggregation of mood disorders was first described by Stenstedt and was subsequently confirmed in several studies. However, numerous possible confounding factors have not been adequately addressed in those studies including: recurrence, comorbidity, biased recall, and personality factors. Moreover, the conclusions of the studies have been based on a dichotomous classification of the age of onset of probands, rather than on significant correlations between the age of onset of probands and relatives.

SEX OF PROBAND The effect of the sex of the proband and relative has been systematically investigated for both bipolar and major depressive disorder. In general there is little deviation in family study data from the sex ratio for bipolar disorder and major depressive disorder reported in epidemiological studies. The rates of occurrence of bipolar disorder are nearly equal in male and female relatives, whereas there is a female preponderance of mood disorders among the relatives with major depressive disorder. However, the transmission of both bipolar disorder and major depressive disorder has been shown to be unrelated to the sex of the proband, with equal rates of mood disorders among the relatives of male and female bipolar disorder and major depressive disorder probands.

In summary the family studies of bipolar disorder and major depressive disorder demonstrate a strong degree of familial aggregation of both mood disorders. However, the evidence is inconclusive regarding the role of shared underlying factors in the expression of the disorders. The transmission of mood disorders appears to be associated with an early age of onset of mood disorder in probands, bipolar disorder, and major depressive disorder with recurrent episodes, but not with the sex of the proband.

MODES OF TRANSMISSION OF MOOD DISORDERS No single mode of transmission of either bipolar disorder or major depressive disorder has been consistently reported. Of the more than 25 segregation and pedigree analyses of patterns of familial transmission of the mood disorders, few studies have reported an adequate fit of the observed familial transmission data to the predictions of most of the traditional genetic models. The threshold models have been found to provide the best fit to the data, with two threshold models for polarity, or two for sex, being the most consistently nonrejected hypotheses. Bipolar disorder is the only mood disorder for which there is an approximately 50 percent decrement in the risk of depression by the degree of relationship to the proband. However, the average recurrence risk of bipolar disorder in first-degree relatives (five percent to 10 percent) is far lower than the 50 percent risk predicted by single major genes with high penetrance as a causative factor. In a 1982 review of the aggregate data on the transmission of bipolar disorder Risch and Baron concluded that the data did not deviate from the expectations of X-linked transmission recessive inheritance because of the low frequency of father-to-son transmission and because the sex ratio seems equal. However, a recent review of the X-linkage studies of bipolar disorder revealed that few of the pedigrees exhibited the hallmarks of X-linked transmission for segregation: that is, a lack of occurrence in offspring of affected males. Moreover, several of the pedigrees used to analyze X-linkage include instances of possible male-to-male transmission.

TWIN STUDIES OF MOOD DISORDERS Numerous studies have compared the rates of mood disorders among monozygotic

and dizygotic twins. The majority of the earlier studies selected probands from inpatient settings or treatment registries. Table 16.4-4 reviews data on the twin studies of probands with bipolar and major depressive disorder in which there were at least 15 twin pairs. The average concordance for mood disorders among monozygotic twins was 60 percent and that for dizygotic twins was 12 percent. There is a fivefold greater rate of concordance for mood disorders among monozygotic than dizygotic twins, thereby indicating the importance of the role of genetic factors in the familial aggregation of bipolar disorder.

There are two recent twin studies of major depressive disorder defined according to criteria of the third edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) or the revised third edition of DSM (DSM-III-R). The evidence for the role of genes in the cause of major depressive disorder is much weaker than for a genetic role in bipolar disorder. The relative risks, comparing monozygotic and dizygotic twins in the two studies, were 1.9 and 1.2, respectively. Nevertheless, the application of quantitative models that estimate the relative components of the variance attributable to shared genes, common environment, or unique nonshared environment yielded significant degrees of heritability in both studies (.39 in the former and .84 in the latter). Differences in the results of the two studies could be attributable to difference in sampling (hospitalized patients were included in the study by McGuffin and colleagues; only women from the general population were included in the study by Kendler and colleagues) or to other methodological differences.

Early studies of the specificity of transmission of polarity in twin studies were reviewed by Edith Zerbin-Rüdin in 1969. The largest twin study that systematically investigated differences in concordance among bipolar and unipolar twins was presented by A. Bertelsen and colleagues in 1977. Table 16.4-5 presents a summary of the studies that examined the concordance rates among twins by polarity. The data provide support for a strong degree of specificity of transmission of the two mood disorders, with little cross-transmission between bipolar disorder index twins with major depressive disorder cotwins, and the converse. The average relative risk for cross-transmission for probands with either depressive or bipolar disorder was 1.5. In contrast, bipolar disorder was found to exhibit a strong degree of specificity, with an eightfold greater risk of bipolar disorder occurring among the cotwins of bipolar monozygotic probands compared with occurrence in their dizygotic counterparts.

The major conclusion that can be drawn from the current evidence from twin studies is that mood disorders are strongly heritable, with bipolar disorder exhibiting a much greater degree of involvement of genetic factors in its etiology than major depressive disorders. Moreover, there is little evidence for the cross-transmission of the two mood disorders. One study calculated the aggregate variance components from the twin studies of major depressive disorder then available and found a significant degree of heritability (.51), a significant contribution of the common environment of the twins (variance, .42), and nearly no effect of the unique environment in the development of mood disorders. Twin studies of milder mood disorders are difficult to interpret because of differences in diagnostic definitions and inconsistent application of the criterion of hospitalization for mood status.

ADOPTION STUDIES OF MOOD DISORDERS Adoption studies are the most powerful design to test the relative contributions of genetic and environmental factors to the causation of the mood disorders. The small number of adoption studies regarding mood disorders is surprising if one considers the rich adoption data on schizophrenia. Of the four adoption studies of mood disorders, three examined the rates of disorders in the biological and adoptive parents of affected and nonaffected adoptees, and only one had bipolar disorder subjects. Two of the three studies yielded strong evidence for transmission of mood disorder after adoption irrespective of the degree of exposure to the biological affected parent (Table 16.4-6). The study by Julien Mendlewicz and John Rainer in 1977 examined both bipolar disorder adoptees and bipolar disorder nonadoptees to control for the factors associated with adoption that may bias

TABLE 16.4-4
Studies of Mood Disorders in Twins*

Author and Year	Monozygotic No.	Monozygotic % Concordance	Dizygotic No.	Dizygotic % Concordance	Relative risk
Bipolar Disorder					
Rosanoff et al (1935)	23	70	67	16	4.4
Kallman (1953)	27	93	55	24	3.9
Harvald and Hauge (1965)	15	67	40	5	13.4
Allen et al (1974)	15	33	34	0	—
Bertelsen et al (1977)	55	51	11	14	3.6
Major Depression					
McGuffin et al (1991)†	62	53	79	28	1.9
Kendler et al (1992)†‡	590	48	440	42	1.2

*Studies with ≥ 15 twin pairs.
†Women only.
‡DSM-III-R criteria.

TABLE 16.4-5
Specificity of Twin Concordance Rates by Polarity

Index Twin	Co-Twin	Monozygotic No.	Monozygotic % Concordance	Dizygotic No.	Dizygotic % Concordance	Relative Risk
Bipolar	Bipolar	42	39	4	5	7.8
	Unipolar	13	12	7	9	1.3
Unipolar	Bipolar	4	11	1	6	1.8
	Unipolar	15	43	3	18	2.4

Data compiled from Zerbin-Rüdin E: Zur genetik der depressiven erkrankurnen. In *Das depressive Syndrom*, H Hippius, H Selbach, editors, p 37. Urban and Schwarzenberg, Berlin, 1969; Bertelsen A, Harvald B, Hauge M: A Danish twin study of manic-depressive disorder. Br J Psychiatry *130:* 330, 1977.

TABLE 16.4-6
Adoption Studies of Mood Disorder

Author and Year	Study Population	% Mood Disorder in Parents: Biologic	% Mood Disorder in Parents: Adoptive
Mendlewicz and Rainer 1977	29 bipolar disorder adoptees	31	12
	31 bipolar disorder nonadoptees	26	—
	22 normal adoptees	2	10
Von Knorring et al 1983	56 adoptees	5	3
	115 controls	5	—
Wender et al 1986	71 adoptees	29	6
	75 controls	5	4

the results. The study reported nearly identical rates of mood disorders among the biological parents of the bipolar adoptees and nonadoptees: 31 percent and 26 percent, respectively. That indicates that the adoptees do not comprise a biased sample with respect to the development of mood disorders. The rate of depression among the biological parents of the control adoptees was only 2 percent, nearly 15 times less than the rates reported among the parents of bipolar disorder subjects.

Paul Wender and associates in 1986 reported the results of a similar adoption study of bipolar adoptees compared with control adoptees. In accordance with the results of Mendlewicz and Rainer, Wender found that whereas 29 percent of the adoptees of biological parents with mood disorder developed mood disorders themselves, only 5 percent of the parents of control adoptees reported mood disorders. Rates of mood disorders in the adoptive parents were also low: 6 percent and 4 percent, respectively. Therefore both studies provide strong evidence of the role of genetic factors in the pathogenesis of mood disorders. The only exception to the positive adoption studies was the 1983 study of Anne-Liis Von Knorring and colleagues, which revealed no evidence of transmission of mood disorders among parents with the condition and their adopted offspring.

Only a single study (Table 16.4-7) employed the adoption study paradigm in which the rates of disorders among the adopted offspring of biological parents with and without mood disorders were investigated. The number of cases was small. The study showed that major depressive disorder among adoptees was positively, but not significantly, associated with a biological background of major depressive disorder. Instead, several environmental factors in the adoptive home, such as death of an adoptive parent before the child reached age 19, or the presence of a behavioral disturbance in a member of the adoptive family, seemed to be related to a predisposition to depression in the adoptee. Nevertheless, the data provide preliminary support for a moderate role of genetic factors in the cause of mood disorders.

The aggregate data from adoption studies of mood disorders clearly indicate that genetic factors are involved in the causation of mood disorders, but that the moderate degree of concordance between biological parents and their adopted-out offspring suggest that common environmental factors also contribute to the expression of mood disorders.

STUDIES OF GENETIC MARKERS

ASSOCIATION STUDIES OF MOOD DISORDERS

Methods The search for markers for the mood disorders has been under way for nearly 40 years. A trait must meet the following criteria in order to be constituted a biologic marker: (1) it should be associated with an increased risk of illness; (2) it should be observable during phases of illness or recovery; and (3) it should be shown to be independent of treatment. Genetic markers are a specific class of biological markers that exhibit clear mendelian modes of inheritance, may be assigned or are assignable to a specific chromosomal location, and are polymorphic, with at least two alleles with a gene frequency of at least 1 percent.

TABLE 16.4-7
Percentage of Mood Disorders in Adopted Offspring by Parental Diagnostic Status

Adoptive Parent	Number	% Mood Disorder in Adoptees
Mood disorders	8	38
Other psychiatric disorders	75	5
Controls	43	9

Data compiled from Cadoret R J, O'Gorman T W, Heywood E, Troughton E: Genetic and environmental factors in major depression. J Affective Disord 9: 155, 1985.

Association studies investigate the relationship between disease status and a particular marker or allele across families and individuals. Most association studies employ the traditional case-control design in which the prevalence of a putative disease marker is compared among persons with a disorder and persons without the disorder. The most common methodological error in association studies is the lack of equivalence between the cases and controls on factors that may confound the association between the purported marker and disease.

After exclusion of spurious associations resulting from methodological factors or population stratification, associations between a disease and a marker could be attributed to either linkage disequilibrium between genes for the disease and for the marker, or the effect of a single gene that encodes both the marker and the disease.

The loci for several biochemical parameters that are suspected to be involved in either the cause or outcome of psychiatric disorders have been identified. However, many of those assignments are based on a single study, and replication is clearly necessary. Identification of new loci is occurring at such a rapid rate that it is necessary to update the human map monthly. It is estimated that more than 10,000 gene loci will have been assigned to particular sites on chromosomes by the year 2000. Application of the methodology to investigations of psychiatric disorders may be particularly fruitful in identifying major genes that are segregating in informative families.

Review of evidence: association studies There have been numerous studies of associations between biological markers and mood disorders. In the past the general approach was to study the relationship between the expression of a known genetic factor at a particular locus and disease status among probands, their relatives, and the general population. The most commonly studied genetic traits have been the human erythrocyte blood groups (ABO), the human leukocyte antigens (HLA), and the enzyme monoamine oxidase (MAO). The results of association studies regarding mood disorders have been inconsistent. There are no markers for which significant associations have been found in more than a handful of studies.

The association between MAO and all of the major psychiatric disorders has been widely studied. Two major forms of MAO have been studied in human populations: MAO_A, in plasma, and MAO_B, in platelets, with varying proportions in most tissues. Low levels of plasma MAO have been reported for major depressive disorder and bipolar disorder. The lack of specificity for a particular disorder suggests that the enzyme cannot be used to identify susceptibility to a specific disorder. Rather, it may be a nonspecific response to dysregulation of another neurochemical system. Furthermore, there may be little or no relationship between the activity of MAO in brain and the periphery of humans, because of the possibility of the involvement of different genes, or differential regulation in the central nervous system than in the periphery. This principle may also apply to other neurotransmitters, neuromodulators, hormones, and enzymes as well. That underscores the importance of including subjects with other psychiatric illnesses as controls, in addition to mood disorder controls, when studying associations between markers and a particular psychiatric disorder. A recent review of biological markers for depression concluded that the most promising candidate biological markers are rapid-

eye-movement sleep, cation transport, and blunted growth hormone response to clonidine.

In contrast to earlier studies, which relied on the expression of inferred underlying genetic mechanisms, it is now possible to apply the techniques of molecular biology to study biological markers in psychiatry. Several recent studies have investigated the association between bipolar disorder and specific DNA markers including tyramine hydroxylase gene on chromosome 11p4 and the dopamine receptor genes on chromosome 5q as shown in Table 16.4-8. Lionel C. C. Lim and associates recently reported confirmation of earlier associations between MAO_A activity and bipolar disorder using DNA polymorphisms. A study of the association between bipolar disorder and the dopamine type 1 (D_1) receptor gene on chromosome 5q and the dopamine type 2 (D_2) receptor gene on chromosome 11q revealed no significant difference in the proportion of cases and controls with specific alleles of the D_1 and D_2 receptor genes. Although one study reported an association between bipolar disorder and the tyramine hydroxylase gene and on chromosome 11p, numerous other studies have failed to replicate the finding. Likewise, studies of other markers yielded no significant association with bipolar mood disorder.

Despite the inconsistent findings of the association studies conducted thus far, the study paradigm comprises an important strategy for identifying genes that may be involved in the cause of the mood disorders. A 1991 study noted that the application of molecular genetic techniques to association studies of depression could actually yield more information than linkage studies regarding the specific functions of genetic abnormalities that contribute to the cause of depression. Moreover, studies of the molecular mechanisms of state markers could yield valid information on the cause of particular symptoms.

LINKAGE STUDIES OF MOOD DISORDERS

Methods Linkage is based on the principle that two genes that lie in close proximity on a chromosome are transmitted to their progeny together. However, if the loci are far apart, crossing-over between the maternal and paternal chromosomes may take place during meiosis, thereby producing new combinations of alleles. The farther apart the loci, the greater the probability that crossing-over will occur and that the offspring may inherit a recombinant of the two parental chromosomes. Crossovers can be detected by inspection of the maternal and paternal genome; when a particular chromosome is not identical to the parental chromosome, a crossover or recombination between the maternal and paternal chromosomes has occurred.

Linkage studies differ from association studies in that linkage is based on an association between genetic markers and putative disease genes within families, whereas association is the co-occurrence of a marker and disease at the level of the general population. Linkage does not imply that the adjacent gene is etiologically related to the disease, only that it can be used to track possible genes in families. Therefore, one allele at a particular locus may be linked to a disease in some families, whereas the other allele may cosegregate with the same disease in other families. In contrast, associations are detected in case-control studies that compare the prevalence of a marker in patients with a particular illness with the proportion of control subjects who possess the marker. Thus, an association found in patient samples may not extend to their families. For example, a strong association between HLA-DR2 and HLA-DQw1 antigens and narcolepsy has been found in 90 percent of patients with narcolepsy compared with 20 to 35 percent of the general population; however, those markers may not cosegregate with narcolepsy in their families.

TABLE 16.4-8
Association Studies of Bipolar Disorder and DNA Markers

Author and Year	Marker	Association
Todd and O'Malley (1989)	Tyramine hydroxylase	No
Korner et al (1990)	Tyramine hydroxylase	No
Leboyer et al (1990)	Tyramine hydroxylase	Yes
Nöthen et al (1990)	Tyramine hydroxylase	No
Nöthen et al (1992)	Dopamine (D_1) 5q	No
	Dopamine (D_2) 11q	No
Inayama et al (1993)	Tyramine hydroxylase	No
Lim et al (1994)	Monoamine oxidase-A	Yes

Two major methods of genetic linkage analysis are the LOD score method and the sib-pair method, derived from Penrose. The LOD score is defined as the ratio of the logarithmic odds of the likelihood of a linkage between two loci within a pedigree to that of the likelihood of independent segregation of the two loci, or a recombination frequency of 0.5. A LOD score $> +3$ represents a probability of .001 of falsely concluding that linkage exists when it is absent, and a LOD score < -2 indicates significant evidence for a lack of linkage between the putative marker and disease. Scientific evidence for acceptance of linkage between a disease and genetic marker was described by Neil Risch, who stated that in addition to a LOD score $> +3$, a linkage finding should be replicated in a different sample in a different laboratory.

The mood disorder sib-pair method examines the sharing of marker alleles at a locus among affected sibling pairs. The null hypothesis of no linkage specifies probabilities of one quarter, one half, and one quarter for sharing 2, 1, and 0 marker alleles among mood disorder sibling. Excess sharing of two haplotypes (or conversely, diminished sharing of haplotypes) provides evidence for linkage. The sib-pair method is a powerful design if the gene is rare and requires no assumption regarding the mode of inheritance of the disorder.

Although previous linkage studies were hampered by the limited number of known polymorphic markers, recent advances in molecular genetics have resulted in the identification of markers across the human genome. Those markers, restriction fragment length polymorphisms (RFLPs), have enabled geneticists to identify disease loci for several major diseases, with Huntington's disease and cystic fibrosis being dramatic examples.

Designs of linkage studies Linkage studies of psychiatric disorders involve interdisciplinary collaboration and are labor intensive. The studies are comprised of three major components, as illustrated in Figure 16.4-1. Clinical psychiatry is involved in defining the phenotype, in diagnoses in probands and relatives, and in the collection of information on families of affected and unaffected probands. The genetic epidemiology component is engaged in study design, determining the optimal sampling procedures both within and between families, defining the population parameters, and conducting statistical analyses of the data. The role of the molecular geneticist is the definition of the genotypes through application of the methods of molecular biology.

In 1988 a workshop on "Linkage and Clinical Features in Affective Disorders" was organized and supported by the MacArthur Foundation, Mental Health Research Network I on the Psychobiology of Depression, in order to review the status and methodology of the linkage studies of mood disorders available at that time. The group examined the comparability of studies in the published literature, identified the major features of mood disorders that were hampering linkage studies, and identified

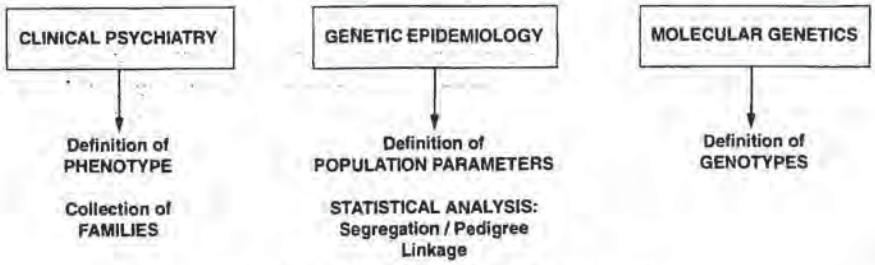

FIGURE 16.4-1 *Major components of linkage studies.*

several key analytical questions regarding mood disorders that needed to be studied thoroughly. The recommendations regarding standards for linkage studies of psychiatric disorders are summarized in Table 16.4-9. Another Task Force was subsequently convened to investigate the specific analytical issues through simulation and theoretical studies. A summary report of the results and recommendations of that group has recently been published.

ETHICAL ISSUES As in any family study of psychiatric disorders, ethical issues apply to genetic linkage studies as well. However, the complexity of the goals and findings of linkage studies require more thoughtful explanations than those of family studies. The results of linkage studies could be easily misinterpreted by the lay audience as implying that the gene that causes bipolar disorder will be identified in specific families. Whereas the sample in family studies usually consists of a large number of nuclear families, linkage studies are often limited to a few large families. Confidentiality is critical and must be maintained, particularly in linkage studies of extended pedigrees that may possess identifying characteristics.

A recent review of the ethical issues in linkage studies enumerates and discusses the following issues in genetic linkage studies: protecting the privacy of the proband in the ascertainment process; opposition by one relative to contact another; specific problems associated with informed consent; and therapeutic intervention. Those are best avoided by the use of experienced clinical interviewers who can explain the specific implications of the study and the importance of the cooperation of as many relatives as possible. Rather than completing a diagnostic evaluation, drawing blood, and thanking the subjects, the investigator should include resources necessary to assist the family members in need of treatment or facilitate contact with mental health professionals, provide results of the individual diagnostic evaluations to treatment professions (on request of the subjects), and supply a personally written letter to convey the results of the study findings to the subjects at their request. Such interaction enhances the relationship between subjects and research staff.

Review of evidence The sib-pair method has been applied extensively to investigate the association between HLA haplotypes and mood disorders (Table 16.4-10). The majority of studies do not provide support for linkage between HLA markers and mood disorder. Only two studies yielded significant findings for a positive association, whereas eight other studies concluded that there was either no association or a negative association between mood disorder and HLA. Despite the negative findings to date, the use of DNA markers as candidate genes in association studies may yield information of the involvement of specific genes in mood disorders. In general, however, the power of association studies is lower than that of linkage studies.

TABLE 16.4-9
Recommended Standards for Linkage Studies*

Advance specification of specific phenotypic definitions
Clear description of ascertainment strategies of probands and relatives
Systematic assessment of both paternal and maternal lines of the pedigree
Collection of extensive clinical information on all members of pedigree
Application of consistent diagnostic criteria, instrumentation, and procedures across studies
Maintenance of blindness to marker and diagnostic status of probands and relatives
Inclusion of sufficient information on methods in publication to allow replicability
Use of longitudinal study designs to validate diagnoses

*Modification of Recommendations of Task Force on Linkage Studies of Affective Disorders Sponsored by MacArthur Foundation Network I on the Psychobiology of Depression and Other Affective Disorders. Arch Gen Psychiatry *46:* 1137, 1989.

TABLE 16.4-10
Sibling Pair Linkage Studies of Mood Disorders: HLA

Author and Year	No. of Pairs	Source	LOD Score
Smeraldi et al (1978)	26	Italy	*
Targum et al (1979)	9	USA	NS†
Smeraldi and Bellodi (1981)	26	Italy	NS
Suarez and Croughan (1982)	26	USA	NS
Kruger et al (1982)	2	USA	‡
Goldin et al (1982)	18	USA	§
Weitkamp et al (1981)	21	USA	NS
Kidd et al (1984)	59	USA	§
Suarez and Reich (1984)	15	USA	§

*> +2
†NS indicates not significant.
‡> +3
§< −2

Linkage studies of pedigrees of probands with mood disorder have focused on X-chromosome markers and those on the short arm of chromosome 11 (Tables 16.4-11 and 16.4-12). Linkage studies of mood disorders and X-chromosome markers were first reported 20 years ago by Theodore Reich and colleagues, who found significant LOD scores between color blindness and affective disorders in two large pedigrees. Subsequent attempts to replicate that finding yielded contradictory evidence; of a total of 10 additional studies of color blindness, Mendlewicz and colleagues and Baron and colleagues confirmed the finding of linkage between color blindness and mood disorders in a total of 28 families. However, subsequent studies of a subset of the same families using DNA markers failed to confirm it. Other X-chromosome markers for which linkage with affective disorders was investigated were the Xg blood group, factor IX,

TABLE 16.4-11
Linkage Studies of Bipolar Disorders: X Chromosome

Author and Year	No. of Pedigrees	Source	Marker	LOD Score*
Reich et al (1969)	2	USA	CB†	‖
Winokur and Tanna (1969)	6	USA	Xg‡	NS
Mendlewicz et al (1972)	7	USA	CB†	‖
Fieve et al (1973)	4	USA	Xg‡	NS
Mendlewicz and Fleiss (1974)	7	USA	CB†	¶
Baron (1977)	1	USA	CB†	‖
Johnson and Leeman (1977)	2	USA	CB†	NS
Gershon et al (1979)	6	USA	CB†	#
Mendlewicz et al (1979)	8	Belgium	CB†	‖
Gershon et al (1980)	16	Europe, USA	CB†	NS
Mendlewicz et al (1980)	1	Belgium (Iranian)	G6PD	¶
Del Zompo et al (1984)	2	Sardinia	G6PD	NS
Kidd et al (1984)	4	USA	CB†	NS
			Xg‡	NS
Mendlewicz et al (1987)	10	Belgium	Factor IX	¶
Baron et al (1987)	5	Israel	G6PD	¶
			CB†	#
Berrettini et al (1990)	9	USA	Xg28	#
Neiswanger et al (1990)§	3	USA	Dxδ52	#
Gejman et al (1990)	1	USA	—	#
Nanko et al (1991)	2	Japan	Xq	NS
Gill et al (1992)	1	United Kingdom	F9	NS
Lucotte et al (1992)	1	France	F9	¶
Curtis et al (1993)	5	Iceland	DBH	#
Bredbacka et al (1993)	1	Finland	F9	#
			DXS548	
Baron et al (1993)	3	Israel	Xq28	#

*Significance of LOD score at $\theta = .05$. NS indicates not significant.
†Color blindness.
‡Xg blood group.
§Major depressive disorder.
¶ > +3.
‖ > +2.
< −2.

G6PD, dopamine β hydroxylase (DBH) and an RFLP marker Xq28. As shown in Table 16.4-11, most of the studies yielded negative results.

The dramatic announcement of linkage between bipolar disorder and the Harvey-*ras* oncogene on the short arm of chromosome 11 in the Amish spurred the current generation of linkage studies of schizophrenia and mood disorders. As shown in Table 16.4-12, all subsequent attempts have failed to replicate the original finding, including reanalyses of the original pedigree with follow-up data and additional extensions of the pedigree. Another recent study of the D_2 receptor gene on chromosome 11 in five Icelandic pedigrees also failed to yield evidence for linkage.

In summary, linkage studies of mood disorder based on inferred expression of an underlying gene through investigation of the phenotype do not consistently support linkage between mood disorders and any genetic marker. A possible exception is the observation of linkage between bipolar illness and loci on the long arm of the X chromosome. Although that too has been controversial, Neil Risch and Miron Baron in 1982 reanalyzed the published studies on X-linkage in bipolar disorder and confirmed that there was a subset of pedigrees in which there was cosegregation for the color-blindness and G6PD loci on the X chromosome and bipolar disorder. Those studies have nearly exclusively focused on probands with bipolar disorder because of the strength of evidence regarding the genetic etiology of the condition. Subsequent attempts to investigate major depressive disorder have also failed to yield evidence for linkage.

CHROMOSOMAL ABERRATIONS The focus on linkage and association studies of psychiatric disorders has led to a relative neglect of studies of possible chromosomal abnormalities that may play a role in their causation (Table 16.4-13). Cytogenetic abnormalities may be of critical importance for identifying regions in which to begin genome searches for linkage and association studies. Stimulated by Ann Bassett's work on chromosomal aberrations in schizophrenia, several investigations have conducted cytogenic studies of bipolar disorder patients. A recent review of that work identified four genomic regions of potential interest including chromosome 11q 21-25, 15q 11-13, 21q, and Xq 28 based on the results of 28 published chromosomal studies of bipolar disorder.

COMPLEXITY OF MOOD DISORDERS

FACTORS INVOLVED IN COMPLEXITY With the aggregate evidence overwhelmingly indicating the involvement of genetic factors in the causation of the mood disorders, why is so little known about their specific role, the magnitude of their contribution, and the mechanisms through which they exert their influence? Moreover, why are the results of the linkage and association so inconclusive?

There are several critical differences between mood disorders and the disorders to which the molecular biologists' tools have been successfully applied. Linkage has been reported for diseases that are extremely rare (<.01 percent population prevalence); exhibit mendelian patterns of inheritance, and are clearly diagnosed with extremely high specificity and sensitivity.

In contrast, the mood disorders are complex disorders, defined as conditions characterized by high population prevalence, a lack of clear distinction between affected and unaf-

TABLE 16.4-12
Linkage Studies of Bipolar Disorders: Chromosome 11

Author and Year	No. of Pedigrees	Source	Marker*	LOD Score†
Egeland et al (1987)	1	USA (Amish)	HRAS INS	§ ‖
Hodgkinson et al (1987)	3	Iceland	HRAS	‖
Detera-Wadleigh et al (1987)	3	USA	HRAS	‖
Gill et al (1988)	1	Ireland	HRAS	NS
Kelsoe et al (1989)	1	USA (Amish)	HRAS INS	NS
Neiswanger et al (1990)†	3	USA	HRAS INS	‖
Mitchell et al (1991)	2	Australia	TH HRAS INS	NS
Mendlewicz et al (1991)	1	Belgium	TH HRAS INS	NS
Holmes et al (1991)	5	Iceland	DRD2 TH	‖
Nanko et al (1991)	2	Japan	INS HRAS	NS NS
Mendlewicz et al (1991)	1	Belgium	INS HRAS	‖
Law et al (1992)	1	Amish	INS HRAS	‖ ‖
Byerley et al (1992)	8	USA	TH	‖
Mitchell et al (1992)	2	Australia	DRD2	‖
Curtis et al (1993)	5	Iceland	TH DRD2	‖ ‖
Kelsoe et al (1993)	3 1	Iceland (Amish)	D2 D11S21	‖ NS
Gurling et al (1993)	6	UK	TH DRD4	NS ‖
Lim et al (1993)	6	Iceland	TH DRD4	NS ‖
Debruyn et al (1994)	14	Belgium	DRD4 TH TYR DRD2 HRAS INS	‖ ‖ ‖ ‖ ‖ ‖

*HRAS indicates Harvey-*ras* oncogene; INS, insulin gene; TH, tyrosine hydroxylase; DRD2 (4), dopamine receptor gene; TYR, tyrosinase; +, nonbipolar major depression.
†Significance of LOD score at $\theta = .05$. NS indicates not significant.
§ > +3
‖ < −2

TABLE 16.4-13
Linkage Studies of Mood Disorders: Other Loci

Author and Year	No. of Pedigrees	Source	Chromosome	LOD* Score
Detera-Wadleigh et al (1992)	14	USA	5q	†
Mitchell et al (1993)	9	Australia	3q13	†
(1992)	2	Australia	5q (DRD1)	†
Eiberg et al (1993)	2	Denmark	16p13	‡
Curtis et al (1993)	5	Iceland	8q 5q 9q	† † †
Coon et al (1993)	8	USA	5q	†

*Significance of LOD score at $\theta = .05$.
† < −2.
‡ > +2.

fected (with the threshold for case definition being somewhat arbitrary), and failure to adhere to mendelian patterns of transmission. The high frequency of the mood disorders in the general population complicate analyses of familial aggregation and patterns of transmission. Even bipolar disorder, which is believed to be a rare condition, is considered to be common by geneticists, who generally deal with conditions with prevalence rates that are 10 to 100 times less frequent than 1 percent. The high prevalence of the conditions in a population increases the probability that family members of both patients and controls will exhibit mood disorders by chance, thereby making it more difficult to discriminate between true cases and phenocopies (that is, persons who express the disease but do not possess the underlying genetic factors).

Despite the inclusion of bipolar disorder as an X-linked disorder (#30920) in the catalogue of *Mendelian Inheritance in Man*, the aggregate evidence from segregation analyses does not consistently reveal evidence favoring any specific mendelian pattern of transmission over another. Nevertheless, convergent evidence suggests that the mood disorders, and bipolar disorder in particular, are familial, with genetic factors playing at least some role in the familial aggregation of the condition.

Other major features of mood disorders that complicate genetic analyses are (1) lack of valid definition(s) of the phenotype and subtypes; (2) heterogeneity of expression of symptoms, (that is, variable underlying syndromes); (3) nonrandom mating patterns among persons with mood disorders, in which probands with affective disorders are more likely to have a spouse with a mood disorder than predicted by population expectations; (4) co-occurrence of other major psychiatric disorders, including primary anxiety disorders, and substance abuse; and (5) lack of evidence for a specific mode of transmission.

METHODS FOR INVESTIGATING COMPLEX DISORDERS

Such methods are critical not only to the identification of genes, but also to all of the research domains that purport to examine the pathways between the genotype and phenotype, such as neurobiologic, imaging, psychophysiology, or challenge strategies, which may be examining as many disease subtypes as patients. The basic approach of genetic epidemiology is the use of the within-family design to minimize the probability of heterogeneity, assuming that the cause of a disease is likely to be homotypic within families. This design reduces or eliminates the danger of genetic heterogeneity that is likely to characterize the mood disorders.

A recent study, in which the results of complex segregation analyses were consistent with a single recessive gene for attending medical school, serves as a reminder of the dangers of overeager acceptance of simple explanations of the transmission of complex phenotypes. The study concluded that the application of segregation or linkage analysis are not a panacea for the problems of complex phenotypes and that the formulation of genetic studies must be developed in the context of information gleaned from the application of classical methods of genetic epidemiology including family, twin, and adoption studies.

IMPLICATIONS OF GENETIC EPIDEMIOLOGIC STUDIES IN PSYCHIATRY

A summary of the clinical and research applications of linkage studies in psychiatry is presented in Table 16.4-14.

TABLE 16.4-14
Application of Linkage Studies in Psychiatry

Identification of aberrant expression or regulation of a gene
Genetic counseling
Identification of subtypes of disorders
Understanding effects of neuropsychopharmacology
Identification of the role of environmental factors

CLINICAL IMPLICATIONS Inquiry regarding the family history is an important component of a thorough clinical evaluation of a patient. Because of the high proportion of false-negative rates in family history studies, information from knowledgeable informants is the best way to enhance the quality of family history data. Several studies have shown that proper collection of family history requires inquiry about each of the first-degree relatives individually, and specific patterns of symptoms and longitudinal course should also be elicited, rather than a global history of the presence or absence of mood disorder.

Because mood disorders are not genetically lethal or associated with a strong increase in mortality, genetic counseling is rarely appropriate for the condition. However, patients may sometimes seek advice regarding the risk of depression in their offspring. In the absence of any genetic or trait markers for depression, such advice should be based on the aggregate data on the familial transmission of depression. Risk estimates should be based on a combination of the age, sex, family history, and risk factors for mood disorders in the individual. Because the mode of transmission of the mood disorders is not known, genetic counseling of couples-at-risk now involves specification of the empirical recurrence risks that have been derived from previous studies of the familial transmission of the disorder. The empirical recurrence risk should be refined according to the family's or individual's sociodemographic characteristics such as age, sex, socioeconomic status, and ethnicity, and the consultant's clinical characteristics including age-at-onset, comorbidity, severity of illness, illness in the coparent, and other factors that may be related to transmission of the disorder. It is also important to consider patterns of transmission in previous generations of the pedigree in estimating recurrence risks.

Approximate empirical recurrence risks for mood disorders among the offspring of probands with bipolar disorder is 12 percent, and among those of probands with major depressive disorder, seven percent. Those estimates have been derived from reviews of controlled family studies that specify the risk of recurrence in offspring of one psychiatrically ill parent. When both parents have mood disorders the estimates may double or triple.

The presence of some disorders can be detected in utero by biochemical means if the defect is known, or through linked markers (with a certain confidence level) if the precise defect is not yet known by assessment of markers in the fetal chromosomes. If the ongoing molecular genetics studies of the psychiatric disorders succeed in identifying disease markers, such markers could ultimately be used to detect a disease-predisposing genotype.

Although the mood disorders have been consistently found to be related to major disruption in familial functioning, it has been difficult to identify whether the disruption in social functioning is causal, contributory, or residual to the illness. Nevertheless, such detrimental environments tend to be transmitted through families, and such combinations of vulnerable genotypes and negative environments are likely to interact in increasing the likelihood that offspring will have mood disorders. The results of recent studies of populations at high risk for the disorders may yield information on premorbid indicators that may permit prediction of persons who are likely to develop a particular disorder. To date, there are no consistent premorbid biological trait markers that allow clinicians to identify vulnerable individuals for any of the major psychiatric disorders.

Finally, clinicians are often called on by family members or prospective spouses to provide data on the course of a particular psychiatric illness. Again, a summary of empirical data relevant to that person's combination of demographic, social, and clinical characteristics should be carefully prepared. Unfortunately, the course of psychiatric disorders and their subtypes have been too often neglected in recent systems of diagnostic nomenclature. That is in direct contrast to the diagnostic approach prescribed by Emil Kraepelin, in which the course of illness was considered to be an essential element of diagnostic definitions.

Because treatment response may also be similar in families, knowledge regarding the treatment history may provide important information in decisions regarding choice of treatment modalities. For example, C.M.B. Pare and J.W. Mack found that relatives of probands with mood disorders shared the pattern of drug response or nonresponse with the proband. In eliciting a family history of a psychiatric disorder, clinicians should also examine the efficacy of specific pharmacological agents among other family members with similar psychiatric syndromes to the patient under evaluation. The application of such information may conserve considerable time and effort in treatment decisions.

RESEARCH IMPLICATIONS In terms of research, application of the within-family design can minimize the heterogeneity that is likely to characterize samples of unrelated patients. That approach, which controls for both shared genetic and environmental factors within families, comprises an extremely powerful method with which to identify the underlying neurobiological mechanisms involved in the pathogenesis of the mood disorders. Moreover, application of other genetic epidemiological study paradigms—such as those of discordant monozygotic twins, monozygotic twins concordant for patterns of expression of depression and associated neurobiological abnormalities, half-sibling studies, and migrant studies—may yield important information for classification, course, risk factors, treatment, and ultimately for the cause of the mood disorders.

Another critical complication of family studies in elucidating the role of genetic factors in mood disorders is the focus on the specific symptoms and symptoms clusters, particularly those that can be assessed quantitatively. The use of family study paradigms to examine the specificity of transmission of the components of mood disorders or putative markers is a necessary step before attempting to employ linkage analyses of the pedigrees. Moreover, the data may also be required for the development of definitions of mood illness and its subtypes, for which the lack of validity appears to be the rate-limiting step in applying the powerful tools of molecular biology and statistical genetics.

Perhaps the most important long-term implication of linkage studies is the potential for identifying individuals with vulnerability to a particular disorder. That would permit identification of the role of environmental factors in either protecting or enhancing the expression of a mood disorder in vulnerable persons. At the same time, there is great danger in the future ability of such studies to identify DNA markers for psychiatric illness. Although such markers comprise valuable indicators of vulnerability, they also could be potentially used as negative labels resulting in social and occupational discrimination.

RECOMMENDATIONS FOR FUTURE RESEARCH

VALIDATION OF DIAGNOSTIC CATEGORIES OF MOOD DISORDERS There is an urgent need for evidence regarding the validity of the mood disorders, particularly the milder forms and those which can be measured on a continuum. Genetic-epidemiological studies designed specifically to test the validity

of diagnostic categories and the overlap between comorbid disorders are necessary to define homogenous subgroups to which the tools of molecular biology may be applied.

INTERDISCIPLINARY APPROACH During the coming decade, as the pathways involved in the expression of genes involved in the central nervous system structure and function become elucidated and genetic markers for the mood disorders and categories thereof become available, researchers can routinely investigate the role of such markers in the transmission of the mood disorders and the mechanisms by which those markers exert their influence; furthermore, as the modification of gene expression through the immune and endocrine systems becomes more clearly elucidated, an interdisciplinary approach in the design of genetic studies will be imperative. That approach will permit simultaneous consideration of the roles of genetic vulnerability factors, nontransmissible factors including the biological environment of the individual, and nontransmissible environmental factors in the expression of underlying vulnerability for depression.

STUDY DESIGNS Application of hybrid and novel designs are forthcoming, such as twin and offspring studies, combinations of family and high-risk paradigms, and half-sibling and extended pedigree studies, all of which are not limited to estimating the heritability of particular disorders but also include identification of specific environmental factors that may be involved in the pathogenesis of these diseases. Substantial work in statistical genetics will be involved, together with the development of creative study designs to investigate gene-environment interactions.

GENETIC LINKAGE STUDIES Genetic linkage studies of psychiatric disorders need to be conducted to resolve the discrepant results obtained thus far, particularly for traits with known loci. The linkage studies that employ RFLPs or polymorphic markers with no known function should also be conducted on selected large pedigrees with clear segregation patterns. Collaborative studies will be the most efficient way to unravel the role or roles of genes in the mood disorders through the sharing of resources, laboratory facilities, and methodological standards in order to prevent the repetition of inconsistent findings that have emerged from the past two decades of linkage studies directed by single investigators. The Gene Bank Initiative of the National Institute of Mental Health in the United States and the Network on the Molecular Biology of Mental Illness of the European Science Foundation are examples of the types of collaborative effort that will be necessary to maximize the application of molecular biology to the study of the mood disorders.

SUGGESTED CROSS-REFERENCES

A general review of molecular genetic mechanisms is provided in Section 1.14. Population genetics in psychiatry is discussed in Section 1.15, and genetic linkage analysis of the psychiatric disorders is discussed in Section 1.16. Genetic epidemiological approaches are also discussed in Section 14.5, with reference to schizophrenia.

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16.5
MOOD DISORDERS: PSYCHODYNAMIC ETIOLOGY

GLEN O. GABBARD, M.D.

INTRODUCTION

The terms "affective disorder" and "mood disorder" are often used interchangeably. However, in psychodynamic parlance "mood" and "affect" have somewhat different meanings. "Affect" is a more specific term than "mood," in that affect is a subjective emotion or feeling attached to a specific idea or an internal representation of the self or of an object. By contrast, a mood is a complex internal feeling state that is pervasive, stable, and sustained by the continuing influence of unconscious fantasy.

In any discussion of the psychodynamic causes of depression or mania, one must avoid consideration of the psychodynamic factors in isolation from the biological and neurophysiological factors. Psychological concerns—such as real or imagined loss, failure to live up to one's expectations, and problematic relationships—may trigger neurochemical and neurophysiological changes in the brain that result in significant alterations in the balance of neurotransmitters. Empirical research suggests that, even in severely depressed patients with melancholia, as many as three fourths have experienced a stressful life event in the months preceding the onset of the illness that is deemed causatively relevant by both the patient and a family member or significant other in the patient's life. Hence, one can conclude that in many cases of depression the cause of the illness may be identified in interpersonal, environmental, and psychological stressors and that the pathogenesis involves actual brain dysfunction in response to the causative influences.

Psychosocial stressors and interpersonal events must also be taken into account in treatment. Attention to relationships in a psychotherapeutic treatment appears to have a specific prophylactic effect in preventing relapse. Compliance with prescribed medication may also be influenced by psychosocial factors. The official Depression Practice Guidelines note that psychotherapeutic management should be part of every treatment for depression.

DEPRESSION

Substantial empirical data support the idea that life events and environmental stressors are relevant to the development of clinically significant depression. The loss of a spouse, for example, is the environmental stressor most often associated with the