6

Depression, Mania, and Suicide: Mood Disorders

1. A 43-year-old married woman, the mother of two children, ages 21 and 18, consulted her physician at the urging of her husband. She complained of fatigue, headaches, and vague aches and pains in many parts of her body. She had developed progressive difficulty in sleeping over the last month or so, with the onset of the vague symptoms. She would often wake up at 3:00 A.M. and think about how empty and meaningless life was. She would feel sad and burst into tears, but lately she felt that her tears had dried up. She neglected her personal appearance and seemed to feel extremely guilty about "not being a good mother, or a wife, or even a housemaid." Her sexual activity decreased to zero. In the last month, she lost 15 pounds. When urged to eat, she would say that food had no flavor, like cardboard. She was also convinced that she had a fatal disease, "Cancer of an internal organ, maybe the stomach." She would not see a doctor, however, because she "might as well be dead, being such a no-good person . . . anyway, the cancer has spread all over me, there is nothing they can do."

2. While making rounds in the morning, a 28-year-old medical resident was noticed to be loud, inappropriate, and irritable. For example, he cracked intimate jokes with the patients in full view of other patients and staff, asked questions of the attending physician in a condescending manner, and proposed radical, potentially dangerous, and unnecessary procedures for the patients. When the proposals were not accepted, he became irritable and accused the others of being incompetent, again in front of patients and staff. When he further stated that he now possessed a secret method of healing that would cure any disease without the need for any diagnostic tests, his colleagues decided that he needed emergency psychiatric help.

On admission, the patient was talking incessantly in a loud voice. He stated to the psychiatrist that he came to the psychiatric unit so that he

could teach the staff how to cure schizophrenia using his secret method. He stated that he would also give electroshock treatments to all the patients on the unit with his bare hands, which were "charged with electricity." He also asked for a dictaphone in his room because he was in the middle of writing five articles at once, including his proposal to the hospital on how to make more money, a "Nobel-prize-winning article on new, secret medical therapeutics for all diseases," and an autobiography. During the first day of hospitalization, he attempted to date all the nurses he saw on the unit.

3. A 64-year-old successful executive of a major company became depressed and despondent after his wife's death about three years ago. His work efficiency decreased, and he began drinking excessively. He often talked about life being meaningless and about how empty success was. The only things in life that really gave pleasure, according to him, were things of beauty, like the collection of original paintings he had in his study, which was his lifetime hobby. For about the last two years, however, he had not purchased any more paintings, which was unusual for him. He had seemed to be especially brooding and generally irritable for about the last three months and was absent from work for several days, which was, again, unusual. Since about a week ago, his spirits seemed to have lifted considerably. He tidied up his office, and he seemed to socialize more, calling up his friends and giving them as gifts his prized painting collection. He even gave his secretary an expensive original painting that was hanging in his office. Last night, he shot himself in the head.

4. A 50-year-old married woman was admitted to the psychiatric unit because of tearfulness, suicidal thoughts, and fatigue. For approximately four or five weeks prior to admission, she had become progressively depressed, with less interest in such activities as watching television, bridge, and reading—all of which she had enjoyed doing in the past. She developed a feeling of impending doom—as though everything would crumble about her. She lost all interest in sex, and food had no taste or flavor. She lost ten pounds during this period. She had difficulty in falling asleep and also in staying asleep through the night. She felt guilty about minor things and felt that she was not a worthwhile person to be allowed to live. She withdrew from her family and friends.

On admission to the psychiatric unit, she was treated with antidepressant medications with equivocal results. She continued to lose weight. A thorough medical workup in the hospital revealed that the patient had a carcinoma of the pancreas. Her depression abated following surgical removal of the diseased pancreas.

5. A few days ago, a 25-year-old medical student began to feel sad, blue, and dejected. He felt like crying from time to time and seemed to feel less pleasure in usual activities. During conversation with a friend, it suddenly occurred to him that the anniversary of his mother's death had just passed. He had been so busy with schoolwork that this had completely escaped his mind. With this recognition, he understood the reason for his sadness.

AFFECT, MOOD, DEPRESSION, AND MANIA

Like anxiety, depression in its milder form is a ubiquitous experience. We feel sad in the face of loss and sometimes helpless and inadequate when we realize that we are not up to completing the tasks required of us. On the other hand, when we have accomplished a task well, we feel joyous, and even elated. In the company of a good friend, and perhaps with a glass of good wine, we feel content and euphoric.

The emotional feeling tone of an individual, such as sadness, joy, depression, and elation, is called an *affect* (see Chapter 4 for further discussion of affect or emotion). When the affect is prolonged and colors the whole emotional life of the person, it is called a *mood*. Thus, a person may be in a blue mood, an elated mood, or a depressed mood.

Very simply, one can consider good and bad moods. On the bad side, such descriptions as feeling down, blue, sad, miserable, depressed, down in the dumps, are used, while, on the other hand, one can think of being happy, high, joyous, euphoric, elated, exulted, ecstatic, and manic. While all of us experience varying gradations of these moods, the extremes of moods, the depressive syndrome and mania, are not experienced except in pathological conditions. Thus, they are collectively called mood or affective disorders.

PHENOMENOLOGY OF DEPRESSION AND THE DEPRESSIVE AND MANIC SYNDROMES

The subjective feeling of sadness is the most common experience of depression in everyday life. This feeling is usually experienced after suffering a loss or failure—the loss of a loved one, possession, or prestige. The loss may be purely imaginary, and even the anticipation of a loss may cause sadness. Depression, in this sense, is closely related to grief, the specific emotional suffering related to loss, and separation, a common antecedent to grief. Separation and grieving processes will be discussed in a later section of this chapter.

The term *depression* is a confusing one, because it is used to denote the whole gamut of unpleasant moods, and exactly what degree of severity is referred to is not clear from the term itself. When psychiatrists

use the term "depression," it almost invariably means the *depressive syndrome,* which is very different, indeed, from feelings of sadness associated with, say, the moving away of a good friend. This is somewhat similar to the difference in the use of the term *hypertension* between the lay public and the medical profession. When a patient talks about having "hypertension," he may mean (1) that he has high blood pressure, (2) that he tends to become tense and nervous, or (3) both. Of course, there are precise blood pressure levels and procedures for the diagnosis of hypertension in medicine. What, then, is meant by depression when the term is used in a medical context?

The *depressive syndrome is characterized by a period of either depressive mood* or a *pervasive loss of interest or pleasure.* The patient, as in vignette 1, often feels *sad, hopeless, helpless,* and *empty. Guilt* feelings are prominent, and there is a loss of *self-esteem.* Feeling discouraged and "down in the dumps" is common. The patient typically *withdraws* from family and friends, and activities and hobbies that used to give him pleasure no longer interest him. There is usually some *sleep disturbance,* usually early-morning awakening (EMA), but middle-of-the-night awakening (MNA) and difficulty in falling asleep (DFA) are not uncommon, especially if anxiety is also prominent. *Loss of appetite* is quite common, with concomitant weight loss, although in some patients, there may be an increase in eating with weight gain. The patients often show *psychomotor agitation* or *retardation.* In agitation, pulling out hair, pacing, wringing hands, inability to sit still, incessant talking, and shaking of hands and feet often occur. Psychomotor retardation is characterized by slowing of speech, slowed body movements, or even muteness.

In the depressive syndrome, patients often manifest *cognitive disturbances* (disturbances in thinking). This includes inability to concentrate, indecisiveness, and generally slowed thinking processes. Often, patients feel that they do not have enough energy to think out a simple problem. They feel tired, fatigued, and exhausted in the absence of physical exhaustion. They may experience vague pains, aches, and discomfort, without any physical basis; headaches, toothaches, backaches, and muscle aches are especially common.

Patients often suffer from feelings of *inadequacy, worthlessness,* and sometimes completely unrealistic *low self-esteem.* The smallest task may appear impossible or monumental. There may be excessive guilt feelings concerning current or past failings, most of them minor, or even delusional conviction of sinfulness or responsibility for some untoward tragic event.

Suicidal ideas are frequent and may take the form of fears of dying, the belief that the person himself or others would be better off if he

were dead, or suicidal desires or plans. Often, there is a *diurnal variation*—the symptoms are worse on waking up in the morning and improve slightly as the day progresses.

When the symptoms are mild, temporary improvement often occurs in the presence of positive environmental stimuli. In several cases, the syndrome is not affected by environmental change to any extent. (Specific diagnostic criteria for the depressive syndrome can be found in the section on Evaluation of Depression.)

At the opposite pole of the depressive syndrome in mood is the *manic syndrome.* Just as sadness and grief are experienced by most people from time to time, so do pleasurable moods of euphoria and elation, short of mania or hypomania, fall within the normal range of mood. In euphoria, there is a positive feeling of emotional and physical well-being. In elation, there is a definite feeling of joy with increase in self-confidence, motor activity, and energy level. These states can be induced by drugs such as alcohol, narcotics, and amphetamines.

On the other hand, mania and hypomania (which is a somewhat less severe form of mania), like the depressive syndrome, form a syndrome with definite features and signs. The essential feature of the *manic syndrome* is a distinct period when the predominant mood is elevated, expansive, or irritable and is associated with other symptoms of the manic syndrome. They include hyperactivity, excessive involvement in indiscreet and foolish activities without recognition of the high potential for painful consequences, pressure of speech, flight of ideas, inflated self-esteem, decreased need for sleep, and distractibility (DSM-III-R, 1987).

The patient may describe the *elevated mood* as being euphoric, unusually good, or high. The good mood may have an infectious quality, so that the physician or others in contact with the patient may find themselves feeling expansive and often humorous. The patient may show *indiscriminate enthusiasm* in relating to people or planning things, so that he may start a dozen projects at once, call up distant relatives and bare acquaintances all over the globe, and go on a buying spree. On the other hand, the mood may be characterized by *irritability* rather than joyfulness, especially when the patient's expansiveness is thwarted. The patient then becomes touchy and domineering. The *hyperactivity* is often generalized, including participation in multiple activities that may be sexual, occupational, political, or religious. The patients often have *poor judgment,* and the activities are disorganized, flamboyant, and bizarre (see vignette 2).

Manic speech is usually *loud, rapid,* and *difficult to understand.* It is often full of jokes and puns and is theatrical, with singing and rhetorical mannerisms. In the irritable mood, there may be hostile comments and

angry outbursts. Abrupt changes from topic to topic based on understandable associations and distracting stimuli often occur (flight of ideas). When severe, the speech may be incoherent. Distractibility is usually present.

Self-esteem is usually inflated, with unrealistic and uncritical self-confidence and grandiosity. For example, the patient may give advice on matters about which he has no expert knowledge whatever—such as how to perform an operation or how to run the federal government. Grandiose delusions may occur, such as, "I have a special hot line to God."

When a person has episodes of *both* depression and mania, this is called manic-depression or *bipolar illness.*

SEPARATION, BEREAVEMENT, AND GRIEF

Phenomenology

The phenomenology of acute grief following separation and bereavement has much in common with that of depression. Lindemann (1944) described the symptomatology of acute grief in his classic paper based on bereaved persons, including those who lost their relatives in the Cocoanut Grove fire. The symptoms of normal grief include sensations of *somatic distress* occurring in waves lasting from 20 minutes to an hour at a time, a feeling of tightness in the throat, shortness of breath, frequent sighing, an empty feeling in the stomach, lack of muscular power, and an intense subjective distress described as tension or mental pain. These waves of distress can be precipitated by mere mention of the deceased. There is often a loss of appetite.

In addition to the somatic distress, grieving persons have an *intense preoccupation with the image of the deceased*—to the point where they may look for the deceased person in a crowd or almost feel the presence of the deceased in the room. *Guilt feelings* are also common. The bereaved searches the time before the death for evidence of failure to do the right things. Self-accusation of negligence and exaggeration of minor omissions are common. The bereaved tends to become *irritable and hostile* to friends and relatives who are making a special effort to show sympathy.

There is often a change in the *patterns of conduct.* The bereaved finds it difficult to initiate and maintain organized patterns of activity, simply going through the motions of carrying out normal activity. The bereaved is surprised to discover how large a part of his customary activity was done in some meaningful relationship to the deceased and has now lost its significance. The bereaved feels restless and unable to sit still. He tends to move about in an aimless fashion, as though in search of something to do.

In addition to the five symptoms described by Lindemann to be pathognomonic for acute grief, some bereaved persons develop an *identification* with the deceased, manifested by the taking on of the manner or speech or gait of the deceased or even the development of symptoms of the deceased's last illness in the absence of evidence of the disease.

Course

The *course* of bereavement was studied extensively by Parkes (1972). He described *three phases* of bereavement: the phase of numbness, followed by the phase of pining, followed in turn by the phase of depression.

The first phase described by Parkes, *numbness,* may last for a few hours up to a few days. This phase may be punctuated by moments of panic and distress, including the somatic distress described above. The second phase, *pining,* is characterized by *anxious searching,* with preoccupation with the thoughts and images of the deceased. This phase includes the somatic distress described by Lindemann, as well as feelings of anger and guilt. Guilt alternates with and eventually gives way to feelings of depression. The anxious searching phase peaks in two to four weeks and leads to the phase of *depression and despair.* This period is also characterized by apathy and aimlessness, with loss of patterns of control.

The course of normal acute grief is approximately four to eight weeks (Huston, 1975), but a substantial proportion of the bereaved continue to report distress up to one or two years after the death of a spouse.

Pathological Grief Reactions

Lindemann described two types of pathological grief reactions, the *delayed* grief reaction and the *distorted* grief reaction.

The delayed grief reaction is characterized by a postponement of the grieving process. When a person is in the middle of performing important tasks, or when it is necessary to maintain the morale of others, there may be no overt sign of grief for weeks, months, or even years after the loss. The full-blown picture of acute grief may be precipitated, however, by mention of the deceased or by a situation that reminds the bereaved of the loss. Such precipitating events may be the anniversary of the loss or the individual's attaining the same age as the deceased's at the time of death.

Distorted reactions may occur during any phase of grief or as a delayed reaction. They include overactivity, no sense of loss, the acquisition of symptoms of the last illness of the deceased, severe alteration in relationship to friends and relatives, excessive hostility against specific persons, lasting loss of initiative, self-destructive activities, and the development of the full-blown depressive syndrome.

Separation in Children

Spitz (1942) described the phenomenon of anaclitic depression in infants in the latter half of the first year on separation from their mothers. This syndrome consisted of crying, apprehension, withdrawal, psychomotor slowing, dejection, stupor, insomnia, anorexia, weight loss, and gross retardation in growth and development. "Anaclitic" means dependence, and the depressive syndrome was presumed to be due to the absence of the mother, a figure to depend on.

Bowlby studied the effects of separation from mothers of somewhat older children (Bowlby, 1960; Robertson and Bowlby, 1952) and described three phases. The first is a *protest* phase, characterized by a frantic searching for the mother with restlessness and tearfulness, followed by a *despair* phase in which the child withdraws from others and appears apathetic. Parkes's later staging of the grief reaction in adults, discussed above, has much similarity to these stages described by Bowlby. When the child is reunited with the mother, some children ignore the mother or actively reject the mother for a period. This was called the *detachment* stage by Bowlby.

Although separation in infants results in a syndrome similar to grief in adults, a causal relationship between early separation and later vulnerability to depression is as yet unproven (Akiskal and McKinney, 1975). Further, there is evidence that substitute mothering can, to a large extent, alleviate whatever damage may occur following separation from the mother.

Separation in Infant Monkeys

The separation reaction described by Bowlby occurs in nonhuman primates as well. Separation of seven-month-old infant monkeys from the mother resulted in initial *violent protest* with crying and searching behavior, followed by a *despair* phase with decreased activity, withdrawn behavior, and occasional crying (Figure 9) (Kaufman and Rosenblum, 1967; Seay and Harlow, 1965).

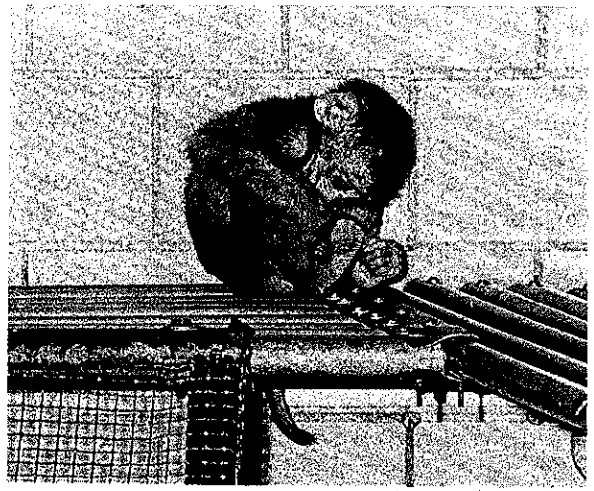

Figure 9. Depressed captive pigtail infant monkey showing characteristic posture of despair including head between legs. (From Kaufman and Rosenblum, 1967. Courtesy of the authors. Reproduced with permission.)

Harlow and Harlow demonstrated the effects of isolation from mothers and peers from birth in rhesus monkeys (Harlow and Harlow, 1962, 1966a, b). The Harlow's experiments showed that tactile sensation was an important element of attachment behavior. Some monkeys were given inanimate "surrogate mothers" made of terrycloth or wire. The infant monkeys would choose "terrycloth mothers," which were mechanical devices with terrycloth, over "wire mothers," which were equipped with a feeding apparatus but without any soft terrycloth. Monkeys that were socially isolated in this way early in life developed difficulties in later life, especially in socialization and sexual activity. These difficulties were alleviated in large measure, however, if peers were present during infancy and childhood.

FUNCTION OF DEPRESSION

The phenomenology of mild forms of depression is indistinguishable from that of grief reactions to losses of varying degrees. Thus, depression as an affect can be conceptualized as a response to loss or separation, actual or symbolic, that may have an adaptive function. The depressive

syndrome, in this light, may be seen as a dysregulation syndrome of the depressive affect.

The feeling of depression signals that a loss or separation has occurred or is in the making. In cases of threatened loss, anxiety will occur together with depressive affect and prepare the individual to deal with the loss (including, in certain instances, avoidance of the loss).

The protest phase of the separation reaction in infants and young monkeys serves the function of drawing the attention of the mother or other members of the social group to the separated infant. The crying of the baby may suddenly remind the mother that it has crawled into another room while she was not watching. *Social support* is often mobilized for an infant who is lost or separated from its mother.

When the separation is prolonged, the infant proceeds into the stage of despair, with reduction in activity and behavioral withdrawal. This state may serve the *conservation* function previously described—in the face of adversity, the organism might withdraw and tend to conserve energy and strength by reduction of activity, so that there might be strength at a later date. Thus, the behavioral patterns of depression may have biologically and socially adaptive functions.

The affect of depression related to helplessness in childhood and threat of loss may play an important role in the *socialization* and *learning* of infants and children. Somewhat like anxiety, which has an optimal level for performance, certain amounts of depressive experience may help the learning process.

SIGNIFICANCE OF BEREAVEMENT, DEPRESSION, AND MOOD DISORDERS

Many recent epidemiological studies indicate that the experience of bereavement or grief is associated with an increased risk of becoming ill or, in fact, dying. Grief was accepted as a cause of death in prescientific medicine, as evidenced by Table 2. The pathophysiological mechanism by which the experience of bereavement, grief, or, for that matter, depression leads to morbidity and mortality by such diseases as coronary disease and cancer remains unclear (see Chapter 4).

The *increased mortality rate* in the bereaved seems to be 2–7 times that of the expected rate in age- and sex-matched nonbereaved persons during the first year of bereavement. The risk of mortality is greater for men than for women for all ages. The major effect of bereavement in terms of mortality seems to occur in the first two years after the death

Table 2. Dr. Heberden's Classification of the Causes of Death in London during the Year 1657[a]

Flox and smallpox	839
Found dead in the streets, etc.	9
French pox	25
Gout	8
Griefe	10
Griping and plague in the guts	446
Hang'd and made away 'emselves	24

[a] As quoted by Parkes (1972), Chapter 2. Copyright 1972 by Tavistock Publications, Ltd. Reproduced with permission from the author and Associated Book Publishers, Ltd., London.

of a spouse and, in men, almost exclusively in the first six months (Jacobs and Ostfeld, 1978). The cause of death of men is accounted for by tuberculosis, influenza and pneumonia, cirrhosis of the liver and alcoholism, suicides and accidents, and heart disease. For women, elevated mortality occurs from tuberculosis, cirrhosis of the liver and alcoholism, heart disease, and cancer.

In addition to increasing the risk of morbidity and mortality from *medical diseases* such as tuberculosis, heart disease, and cancer, *bereavement precipitates a depressive syndrome* in a significant number of persons. Clayton and her associates studied 109 randomly selected bereaved subjects (Bornstein *et al.*, 1973; Clayton *et al.*, 1972). At one month after bereavement, 35% of the sample were definitely or probably depressed; at 13 months, 17%. Thirty-nine percent had a depressive syndrome at some time during the period.

Depression unassociated with bereavement has also been shown to be associated with increased morbidity and mortality. For example, in one study, subjects who had acute myocardial infarction and died had higher depression scores on the Minnesota Multiphasic Personality Inventory (MMPI) than those who had acute myocardial infarction and survived (Klerman, 1989; Lebovitz *et al.*, 1967).

Preoperative depression is known to be a predictor of increased postoperative behavioral problems and mortality in cardiac surgery patients (Kennedy and Bakst, 1966; Reiser and Bakst, 1975). On the basis of studies of illness-onset situations, Schmale and Engel postulate that a feeling of helplessness and hopelessness (the *giving up–given up complex*) may provide a "permissive" setting for the development of a medical disease (Schmale, 1972). This permissive setting, which has many features of de-

pression, was found to occur in patients who had leukemia, lymphoma, diabetic ketosis, cervical carcinoma, bronchial asthma, and other diseases.

In one study, the mortality during the first decade after hospitalization of those who had been admitted to a psychiatric service for depression and mania was more than two and three times, respectively, the mortality rate of control subjects who had been admitted for surgical reasons (Tsuang *et al.*, 1979)

EPIDEMIOLOGY OF MOOD DISORDERS

Just how common are depression and mania? As we discussed, transient depressive or euphoric mood is ubiquitous. What about the depressive and manic syndromes?

In a comprehensive review, Boyd and Weissman (1981) report that the lifetime prevalence of affective disorders in general is 17–20%, and a one-year prevalence is 5–8%. Affective disorders, then, are the most common psychiatric disorders. In the United States and Europe, an estimated 8–11% of male adults and about 18–23% of female adults have had a depressive syndrome at some time. Approximately 6% of the females and 3% of the males have had depression severe enough to require hospitalization. Thus, the sex ratio for depressive syndrome for females and males is 2:1.

As for the bipolar illness, it is estimated that about 0.4–1.2% of the adult population have had at least one manic episode. Unlike the depressive syndrome, bipolar disorder is equally common among men and women.

In an extensive review, Hirschfeld and Cross (1982) described the epidemiological factors that seem to increase the prevalence of affective disorders, which include the full-blown and incomplete depressive syndromes. The incomplete depressive syndrome, which they called "depressive symptoms," was characterized by the presence of dysphoria and was often accompanied by other associated features of the depressive syndrome but did not quite meet the criteria for the complete syndrome (see the criteria in Table 3). Their findings are summarized below.

Sex. Female/male ratio of 2:1 for both complete and incomplete unipolar depressive syndrome. No sex difference for bipolar disorder.

Age. There seems to be a higher prevalence for both complete and incomplete unipolar depressive syndrome in the younger adult age

groups (18–40 years of age) than in older groups. Typical age of onset of unipolar depression is in the late 30s, as opposed to the late 20s in bipolar depression or mania.

Marital Status. Unipolar depression (both complete and incomplete syndrome) is more common among separated and divorced persons, and married groups have the lowest rates. There is no marital-status difference in the prevalence of bipolar disorders.

Residence. Although there is some suggestion that depressive symptomatology is greater in urban areas, there is no conclusive evidence that residence affects the prevalence of affective disorders.

Race. There is no evidence for race differences in affective disorders.

Religion. There is no difference in prevalence of unipolar depression among different religions. However, bipolar disorder has been reported to be particularly common among Ashkenazi Jews and among Hutterites in the northern Midwest.

Social Class. Unipolar depression seems to be more common among persons of lower socioeconomic status. On the other hand, an unusually high rate of unipolar (38–50%) depression has been reported among professional women (Welner *et al.*, 1979). As for bipolar disorder, the rate seems to increase with increasing socioeconomic status, with the highest rates among professionals.

Life Changes. As would be expected, unipolar depression is more common among persons who have had stressful life changes, particularly after bereavement.

Presence of Other Medical and Psychiatric Disorder. Depression is often associated with a medical disease or another psychiatric disorder (e.g., substance abuse).

Significant Others and Family Resources. Significant others and supportive family members seem to provide a protective effect against unipolar depression.

Personality Characteristics. Not surprisingly, the "personality profiles" of patients with unipolar depression show increased introversion, neuroticism, obsessionality, dependency, and low self-esteem. In bipolar

disorder, however, the personality profiles are mostly normal except for higher levels of obsessionality.

BRAIN MECHANISMS OF AFFECTIVE DISORDERS

Certain areas in the brain are known to be associated with the experience of pleasure and displeasure. Among others, electrical stimulation of the medial forebrain bundle is considered to be pleasurable and reinforcing to the animal, while electrical stimulation of the periventricular system is considered to be unpleasant (see Figures 10–12). It is reasonable to suppose, then, that these structures are somehow involved in the experience of mania and depression (Akiskal and McKinney, 1975). The biogenic amines norepinephrine and serotonin are both involved in the modulation of the function of the medial forebrain bundle and the periventricular system.

There is recent evidence that the relative glucose metabolism of the left dorsal anterolateral prefrontal cortex may be reduced on positron emission tomography (PET) in severely depressed patients. This was reversed with successful antidepressant therapy (Baxter *et al.*, 1989; Martinot *et al.*, 1990). General hypofrontality that did not respond to antidepressant therapy was also reported in some depressed patients.

Biogenic Amines

Much information on the brain mechanisms of affect is based on the study of patients with the fully developed depressive and manic syndromes and their pharmacological treatment. The two classes of antidepressants, tricyclics and monoamine oxidase inhibitors (MAOIs), increase the functional levels of biogenic amines in the brain. The biogenic amines thought to be involved in the brain are the catecholamines (mainly norepinephrine and dopamine) and the indoleamine serotonin. Reserpine, used in the treatment of hypertension, depletes biogenic amines (both catecholamines and indoleamines) in the neurons and can cause the depressive syndrome in 10–15% of patients receiving it. The catecholamine hypothesis of depressive disorders (Schildkraut and Kety, 1967) postulated that in mania, there is an increased functional level of norepinephrine in the noradrenergic synapses in the brain, whereas in depression, there is a decreased functional level of norepinephrine in the brain. The cell bodies of the norepinephrine-containing neurons are

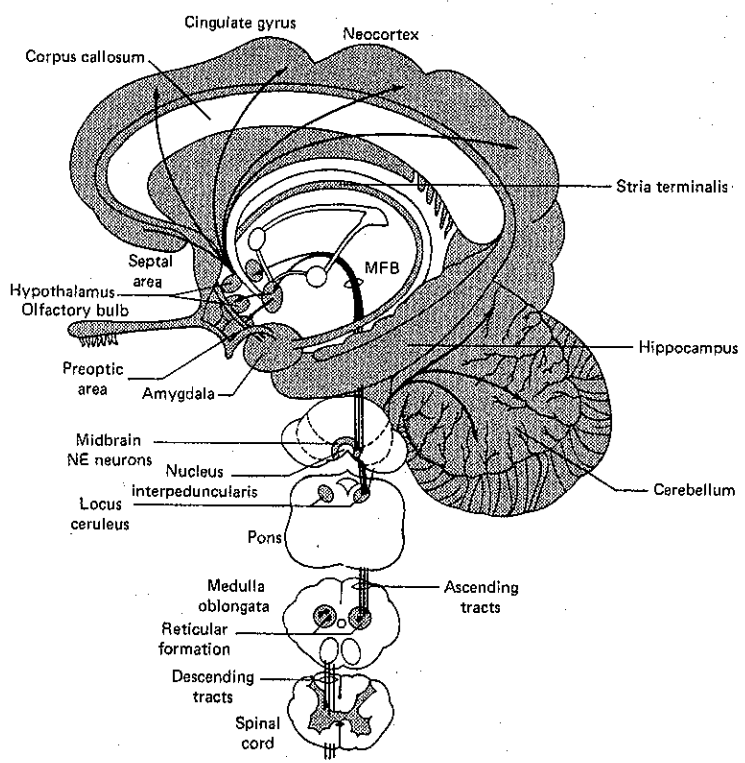

Figure 10. Noradrenergic (NE) systems. Sagittal projection of NE pathways arising from cell groups in medulla oblongata and pons. The NE tracts are both descending and ascending. Descending fibers arise from cell bodies in the medulla oblongata and innervate the gray matter of the spinal cord. Ascending neurons are derived primarily from cell bodies in the medulla oblongata (reticular formation) and pons (locus ceruleus) and enter the medial forebrain bundle (MFB). These fibers innervate the hypothalamus, stria terminalis, preoptic area, septal area, amygdaloid cortex, cingulate gyrus, and neocortex. The cerebellum is also innervated by NE neurons from the medulla and pons. A smaller number of NE neurons arise from an area surrounding the nucleus interpeduncularis. (From *Neuropsychopharmacology, 1: The Monamine Systems, 1976.* Reproduced with permission from Roche Laboratories, Nutley, New Jersey.)

in the brain stem, especially in the locus ceruleus in the pons (see Figures 6 [Chapter 4] and 10). The axons ascend in the medial forebrain bundle to supply the hypothalamus and areas of the limbic system as well as the entire cerebral cortex (Sweeney and Maas, 1978).

The pharmacological evidence may be equally strong for a *serotonin* theory, which is especially widely accepted in Great Britain. The cell bod-

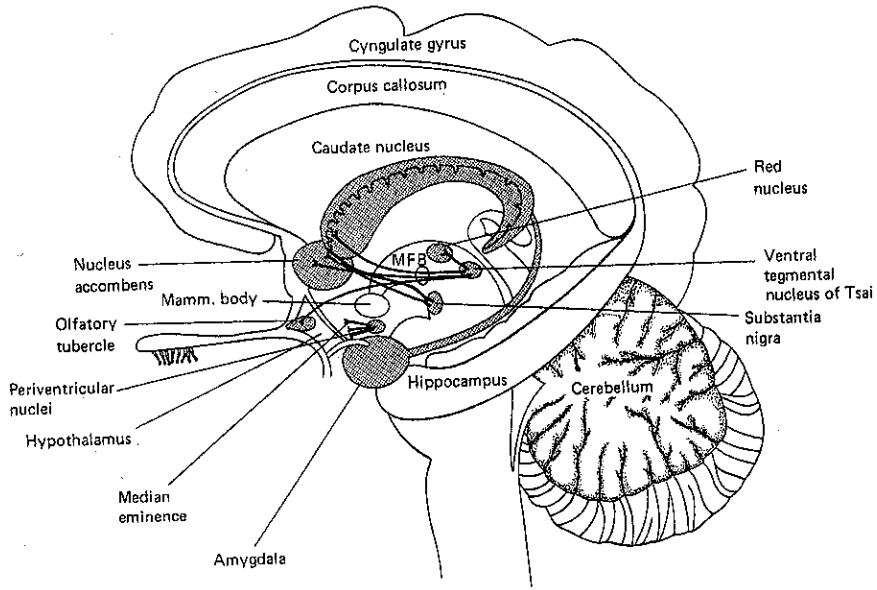

Figure 11. Dopaminergic (DA) systems. Sagittal projection of the DA pathways arising from cell groups in the midbrain. The DA neurons form at least three definable systems. One pathway consists of the nigrostriatal tract, which arises from cell bodies in the substantia nigra and terminates on small interneurons of the neostriatum (caudate nucleus and putamen). (Note: Putamen cannot be seen from sagittal view.) A second major pathway arises from the ventral tegmental nucleus of Tsai (located about the cranial portion of the nucleus interpeduncularis), enters the medial forebrain bundle (MFB), and terminates anterior to the caudate nucleus in the nucleus accumbens (nuclei nervi vestibulocochlearis), olfactory tubercle, and red nucleus of the stria terminalis (the limbic striatum). A third pathway involves DA cell bodies from the arcuate and anterior periventricular nuclei that terminate in the median eminence of the hypothalamus and appear to have a role in regulating gonadotropin secretion. (From *Neuropsychopharmacology, 1: The Monoamine Systems,* 1976, with modification. Reproduced with permission from Roche Laboratories, Nutley, New Jersey.)

ies of the serotonergic neurons are in the median raphe in the mesencephalon and upper pons (Figure 12). Their axons ascend in the medial forebrain bundle, giving off terminals to various parts of the brain, including the hypothalamic areas and the cerebral cortex. There is evidence that depressed patients have low levels of 5-hydroxyindoleacetic acid, a serotonin metabolite, in the cerebrospinal fluid (Åsberg *et al.*, 1973; Bowers *et al.*, 1970). Low levels of serotonin and 5-hydroxyindoleacetic acid were found in the autopsied brains of suicidal patients (Davis, 1977). L-Tryp-

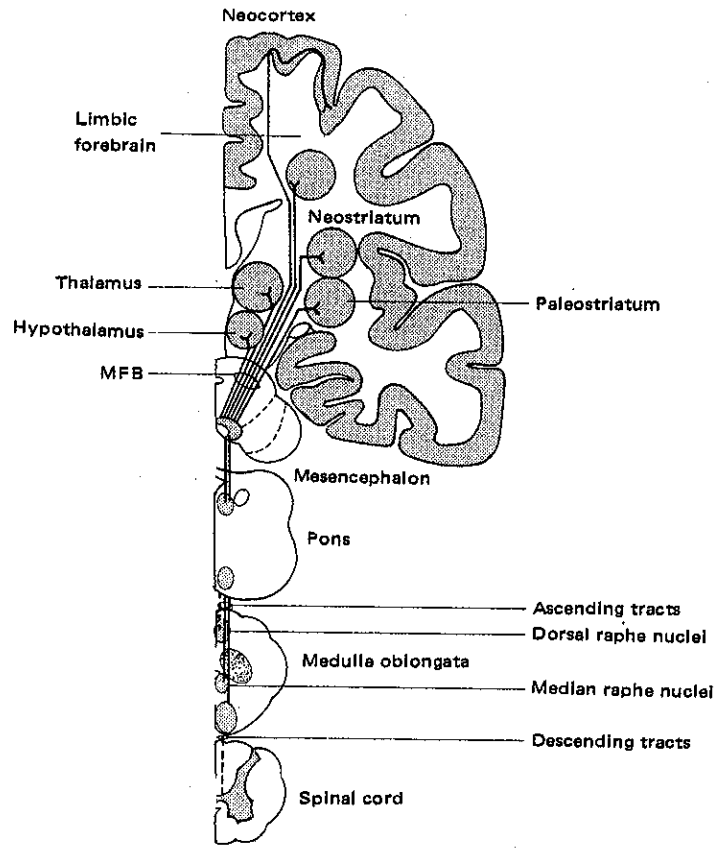

Figure 12. Serotonergic (5-HT) systems. Diagrammatic representation of 5-HT pathways arising in the mesencephalon, entering the medial forebrain bundle (MFB), and innervating rostral nuclei along with NE neurons. The 5-HT neurons tend to have a distribution similar to the NE system. Descending pathways innervate the gray matter of the spinal cord; cell bodies are located primarily in the lower raphe nuclei of the pons. Ascending neurons arise from cell bodies in the medulla, primarily the medial and dorsal raphe nuclei, and accompany the NE neurons to the hypothalamus, limbic forebrain, neostriatum, paleostriatum, and neocortex. (From *Neuropsychopharmacology, 1: The Monoamine Systems,* 1976. Reproduced with permission from Roche Laboratories, Nutley, New Jersey.)

tophan is the precursor of serotonin in the brain, and the brain level of serotonin seems to be determined by the blood level of L-tryptophan. There is evidence that L-tryptophan may improve the symptoms of both mania and depression in some patients (Davis, 1977). Prange *et al.* (1974)

postulated a *permissive theory* of affective disorders that states that in all affective disorders, there is an abnormally *low level of functional serotonin* in the brain; in addition, in the case of *depression,* there is a *decrease* in the functional level of norepinephrine in the brain and in *mania* an *increase* (see Chapter 11 for serotonin's role in sleep).

Other investigators believe that there may be *two different kinds of depressive syndromes,* one associated with *decreased functional levels of norepinephrine* in the brain and the other with *decreased functional levels of serotonin.* The urinary excretion of *3-hydroxy-4-methoxyphenylethylene glycol* (MHPG), a metabolite of norepinephrine largely produced in the brain, is found to be low in some depressed patients, but not in others. Those who have low levels of MHPG tend to respond better to imipramine, a tricyclic antidepressant that increases the brain levels of norepinephrine and, to a lesser extent, of serotonin, whereas those who do not have low levels of MHPG tend to respond better to amitriptyline, a tricyclic that increases brain serotonin levels more than imipramine (Maas, 1978).

More recent studies indicate, however, that the CSF MHPG levels are increased rather than decreased in depressed patients. In addition, the urinary excretion of epinephrine and norepinephrine and their metabolites was increased in depressed and manic patients as opposed to controls (Koslow *et al.,* 1983). Thus, a hyperfunctioning rather than hypofunctioning noradrenergic system is suggested in affective-disorder patients.

Receptor Sensitivity

More recent evidence suggests that changes in the sensitivity of postsynaptic receptors to norepinephrine and serotonin may play a more important role in affective disorders than the functional levels of the biogenic amines (Charney *et al.,* 1981, 1982).

Antidepressant therapy in depressed patients requires several weeks to take effect, while the functional levels of biogenic amines at synapses increase almost immediately following drug administration through the blockade of their reuptake into the presynaptic neuron. Long-term antidepressant therapy has been shown to change the sensitivity of postsynaptic receptors in complex ways: increased sensitivity to serotonin and (α-adrenergic stimulation and decreased sensitivity to β-adrenergic stimulation.

Acetylcholine

In addition to the biogenic amines norepinephrine and serotonin, acetylcholine is also probably involved in depression. There is evidence

to indicate that the brain cholinergic function may be high in depression and low in mania (Janowsky *et al.,* 1972, 1973). Physostigmine, a substance that inhibits cholinesterase, the enzyme that breaks down acetylcholine, was shown to convert mania to depression and to make depression worse.

Thus, three major neurotransmitters in the brain, acetylcholine, norepinephrine, and serotonin, seem to be involved in at least some forms of depression. Another way of conceptualizing the relationship between the neurotransmitters and depression is that the central nervous system must function as a system in which there is an equilibrium of neurons using different transmitters. Such a system may become dysregulated if any of the components malfunction, and the overall equilibrium of the neurotransmitters may shift, producing abnormalities in more than one subsystem. At the same time, in one dysregulated system, one may find particularly reduced function of one component (say, norepinephrine), while in another dysregulated system with the same behavioral characteristic, one may find reduced function of another component (such as serotonin).

Brain noradrenergic function may be reduced in cats in states of heightened emotionality, regardless of whether the state is pleasurable or aversive (Bliss and Zwanziger, 1966; Bliss *et al.,* 1966).

Other Putative Neurotransmitters and Neuromodulators

Numerous other substances, among them the endorphins and enkephalins (see Chapters 4 and 7) and, possibly, histamine, have been suspected of being involved in mood states, but the findings are still too preliminary to warrant full discussion.

Intracellular Sodium

In both depression and mania, there seems to be an increase in residual sodium (intracellular sodium plus the sodium in bone). In depression, the magnitude of increase is 50% and in mania, 100%. This increased intracellular sodium (hypothesized for the brain) may lower resting membrane potential and increase neuronal irritability and thus "arousal." There may be central hyperarousal in both depression and mania, as evidenced by insomnia, especially reduction in the delta (deep) sleep, and lowered threshold for arousal (Whybrow and Mendels, 1969).

Parenthetically, alcohol also increases intracellular sodium and potentially aggravates depression.

Seasonal Depression and Biological Rhythms

Some individuals develop a recurrent depressive syndrome in the fall, which generally remits spontaneously in the spring (Rosenthal *et al.*, 1984). This type of depression is called *seasonal affective disorder* (SAD) or *winter depression*. The syndrome is often associated with hypersomnia and morning drowsiness, weight gain, and low energy. Bright-light therapy has been shown to be effective for this type of depression, especially if given in the mornings (Sack *et al.*, 1990). This may indicate that in the winter depression, some patients may have a delayed circadian rhythm. Morning bright light might advance such a delayed rhythm.

There is evidence that in nonseasonal depression and in bipolar depression, there is a phase advance of rapid eye movement (REM) sleep, temperature, cortisol, and melatonin rhythms compared to the sleep–wake cycle (Kripke *et al.*, 1978; Wehr and Goodwin, 1980). A subset of depressive patients appear to show reduced nocturnal serum melatonin levels ("low melatonin syndrome") associated with abnormal dexamethasone suppression test (DST), a less pronounced daily and annual cyclic variation in depressive symptomatology (Wetterberg *et al.*, 1990). Administration of melatonin does not, however, alleviate the depressive symptomatology in this syndrome (Carmen *et al.*, 1976; James, 1990).

Psychological Aspects

Early psychoanalytic formulations concerning depression focused mainly on object loss and *turning inward of hostility* that had originally been directed toward an ambivalently loved person who had been lost through death or separation (actual, threatened, or symbolic) (Freud, 1917). Later, "ego psychologists" such as Bibring (1965) added the formulation that depression is a state in which the individual recognizes his inadequacy and *helplessness*—loss of self-esteem. Beck (1967) postulates an altered *cognitive style* characterized by negative expectations to be the basis of depressive states. His theory, then, gives primacy to the cognitive or thinking aspects of depression—negative conception of the self, negative interpretations of one's experiences, and a negative view of the future. From these cognitive changes arise helplessness and hopelessness and the mood of depression. The "learned helplessness" model of Seligman (Seligman and Maier, 1967) provides an interesting model for depression. Many animals that had been exposed to multiple sessions of inescapable shock showed impaired ability to avoid shock even when it was avoidable—as though they had "learned" that the shocks were not avoidable.

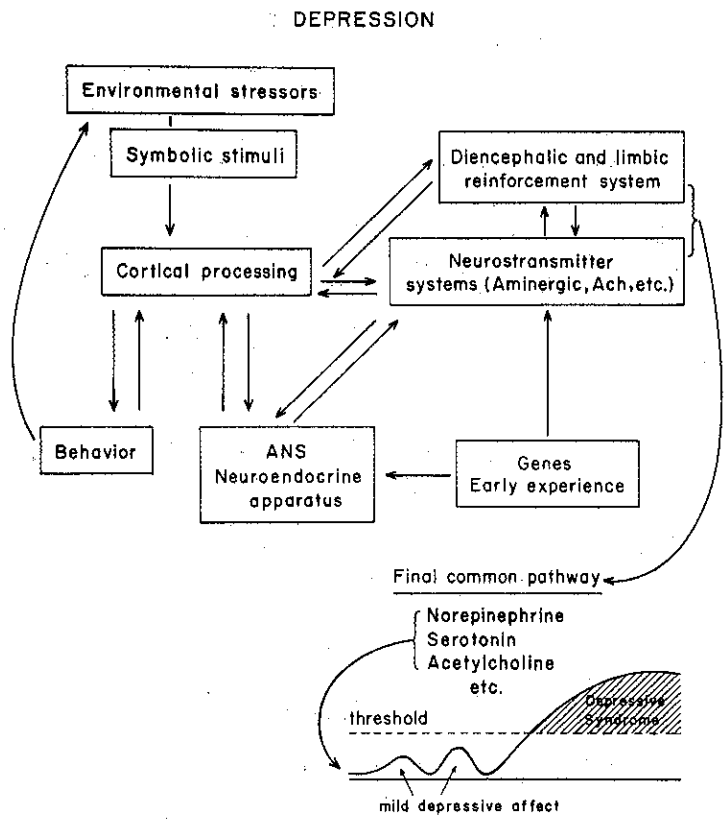

Figure 13. An integrated model of depression.

According to Wolpe (1971), chronic anxiety resulting from chronic frustration in one's personal or professional life causes *hopelessness* concerning the reduction of anxiety. Related to these theories are the observations that antecedent to a depressive episode, there is often a lack of environmental rewards (positive reinforcement) for formerly successful behaviors.

A Hypothetical Integrated Model (Figure 13)

Depression may be conceptualized as expressing a state of the central nervous system with accompanying neuroendocrine and physiological changes. This state of depression may have a *final common pathway,*

which might be the state of brain neuronal systems concerned with reinforcement and pleasure. Environmental, symbolic, and genetic–chemical factors would contribute to and influence this final common pathway to varying degrees. For example, the basic vulnerability of the neurotransmitter (and perhaps reinforcement) systems in the brain may be determined by genetic (and early experiential) factors.

Psychosocial stresses such as separation and loss might be translated in the brain into neuronal impulses and neuroendocrine responses, which in turn may change the activity of neurons in the neurotransmitter and reinforcement–pleasure systems. Vulnerability to depression may be conceptualized as related to a hypothesized threshold in the central nervous system. Given a large *genetic loading* (low threshold) for depression, only a minimal amount of symbolic stimuli may be sufficient to trigger a severe depressive state. On the other hand, in some individuals with no genetic loading (high threshold), even catastrophic losses conceivably might not result in a detectable depressive state. Once a depressive state occurs, it may further aggravate depression through behavioral changes (e.g., social withdrawal) and cognitive changes (e.g., pessimistic outlook).

On the basis of clinical studies, it seems that once a severe *depressive syndrome* has developed, no matter what the precipitating event, it reaches a phase that has an autonomous course that can be modified only by time or somatic intervention, such as antidepressants or electroshock therapy. Thus, one might postulate a threshold for the final common pathway for depression—once the threshold has been reached for the depressive syndrome, a process similar to a stress-induced disease in other organs (such as stress-induced peptic ulcers) may ensue. This threshold might speculatively be related to the functional level and sensitivity of noradrenergic, serotonergic, and cholinergic systems related to reinforcement and pleasure. Seen in this light, depression would be a stress-related disease with the brain as the target organ (Figure 13).

PHYSIOLOGY AND ENDOCRINOLOGY OF AFFECTIVE DISORDERS

Depression is associated with a specific pattern of facial muscular patterning (Izard, 1977) that is identifiable in monkeys and humans and across cultures. This characteristic facial expression, together with the specific behavior patterns (such as protest and despair), is probably associated with the adaptive significance of depression discussed above.

In states of *sadness,* there seems to be agreement that the parasympathetic nervous system is activated, with concomitant physiological alterations. The latter include lacrimation and decrease in blood pressure and heart rate (Izard, 1972). In the *depressive syndrome,* however, the physiological changes are quite complex. In patients with established depressive syndrome, the heart rate may be increased, and increased blood pressure has been associated with depression (Altschule, 1953; Heine *et al.,* 1969). The increased sympathetic activity found in the depressive syndrome may be associated with the central arousal and anxiety that often accompany the syndrome.

Neuroendocrinology

Endocrine changes have been studied primarily in patients with the full-blown depressive syndrome. A number of typical endocrine changes accompanying depression have now been identified, and it is also known that primary endocrinopathies may cause secondary depressive syndromes or depressive symptomatology (see the section on Evaluation of Depression). In general, the endocrine changes found in the depressive disorder (depressive syndrome) are the kinds of changes that might be anticipated on the basis of the effect of functionally decreased levels of brain norepinephrine on the hypothalamic releasing and inhibitory hormones.

Adrenocorticotropic Hormone and Cortisol. Adrenocorticotropic hormone (ACTH) seems to be synthesized and released in response to the hypothalamic corticotropin-releasing factor (CRF). Under normal conditions, CRF secretion appears to be tonically inhibited by the higher brain centers through a noradrenergic (norepinephrine) influence.

In the depressive syndrome, there may be a severe *disinhibition of the hypothalamic–pituitary–adrenal function.* Thus, in depression, there is a marked elevation in the plasma cortisol levels throughout the day and night, obliterating the normal circadian rhythm of cortisol secretion (Ettigi and Brown, 1977; Sachar, 1975). Depressive patients with elevated cortisol secretion often do not show normal suppression of cortisol production after the administration of *dexamethasone,* a potent synthetic corticosteroid. Dexamethasone normally suppresses pituitary ACTH secretion and thus lowers plasma cortisol. The depressive patient's *dexamethasone suppression test* usually returns to normal when depression improves (Carroll, 1972).

Although nonspecific emotional arousal can also result in increased cortisol levels, the increase accompanying the depressive syndrome

seems to be fundamental and not secondary to arousal, as evidenced by elevated cortisol levels in sleeping patients and apathetic patients.

Growth Hormone. Growth hormone secretion is probably controlled by a hypothalamic releasing factor (GHRH) and an inhibiting factor (somatostatin). Growth hormone release normally occurs in response to hypoglycemia, exercise, stress, arginine infusion, and slow-wave sleep.

There is evidence to suggest that catecholamines (norepinephrine and dopamine) mediate growth hormone secretion. In depression, there appears to be a *decreased growth hormone response* to hypoglycemia.

Other Hormones. In addition to corticosteroids and growth hormone, the levels of which are probably altered in depression, other hormone systems, such as luteinizing hormone, thyroid hormone, and prolactin, might also be altered in depression, although this is not yet well established.

The endocrine changes in mania are not well established and are at best controversial.

Physiological Signs of Depression (Depressive Syndrome)

In severe depression (depressive syndrome), there is often a loss of appetite, decreased sexual interest and drive, profound loss of interest in and experience of pleasure, constipation, and weight loss. In some patients, there may be an increase in appetite and weight gain, especially when depression is not severe. Sleep disturbances are common, especially early-morning awakening. There may be profound psychomotor retardation or agitation. Vague physical symptoms such as aches and pains may be present.

EVALUATION OF DEPRESSION

When the physician suspects that a patient is depressed, specific types of further evaluation should be made. The kinds of things the physician must decide in the course of this evaluation are the *severity* and *nature* of depression, *suicidal risk, advisability of hospitalization,* and *management plans.*

We mentioned earlier that depressive affect is usually generated in response to a loss and that it may have adaptive significance. In

cases of mild depression (or, rather, sadness), recognizing the loss suffices in the evaluation, since the loss can be dealt with by the patient alone or with the support of his family, friends, or the physician. The same is true in grief reactions, in which the nature of the loss is clear. Grief reactions often occur in the medical setting in anticipation of the *loss of function* or of an organ, such as in amputations. Grief over the patient's own impending death also occurs. Duration of depression is an important factor to be considered. A patient who has become seriously depressed in the last month, for example, needs a different management plan from another patient who has been depressed for the last five years.

The following specific questions, then, should be answered in the comprehensive evaluation of a patient with suspected depression:

1. Questions concerning the *phenomenology* of depression
   - Sad affect; loss of interest
   - Difficulty with concentration
   - Crying
   - Guilt feelings
   - Hopelessness and helplessness
   - Low self-esteem
   - Decreased libido
   - Anorexia
   - Constipation
   - Dry skin
   - Dry mouth
   - Vague aches and pains
   - Sleep pattern
   - Suicidal thoughts or plans
2. Observation of *behavior and appearance*
   - Sad or apathetic appearance
   - Evidence of self-neglect
   - Agitation or psychomotor retardation
   - Cognitive disturbances
3. Questions concerning *history of depression*
   - Duration of the depression
   - Past history of depression or mania
   - Family history of depression, mania, suicide, or alcoholism
4. Questions concerning *medical history*
   - Possible concurrent disease
   - Drugs

Table 3. Diagnostic Criteria for Depressive Syndrome[a]

At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucinations, incoherence, or marked loosening of associations.)

1. Depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day
2. Marked diminished interest or pleasure in all, or almost all, activities of the day, nearly every day
3. Significant weight loss or weight gain when not dieting (e.g., more than 5% of body weight in a month)
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agigation or regardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

[a]From the DSM-III-R. Reproduced with permission, with minor modifications, from the American Psychiatric Association.

5. Questions concerning *environmental factors*
   Losses
   Separations
   Anniversary of above

Once mild sadness and grief reactions have been ruled out, the physician should determine whether the depression is *chronic or acute.*

Chronic depressive disorder (dysthymic disorder) is defined as moderate to severe depression with a duration of *longer than two years without remission.* With these patients, sad feelings and some of the other psychological and physiological signs of depression seem to be a *character style.* Depression in this case, then, is a trait that cannot be expected to be easily removed by treatment.

If the patient's depression does not fall under the chronic depressive disorder, then the presence or absence of the depressive syndrome (depressive episode) has to be determined. An acute *depressive syndrome* can be diagnosed by the criteria shown in Table 3.

Once the diagnosis of *depressive syndrome,* complete or partial (although not all criteria are met, sufficient criteria are fulfilled to cause

Table 4. Partial List of Medical Conditions Often Associated with Depression

Endocrinopathies
Hyperparathyroidism (hypercalcemia)
Cushing's syndrome
Hypothyroidism
Premenstrual tension syndrome
Viral disease (often during incubation and convalescence)
Influenza
Infectious mononucleosis
Infectious hepatitis
Any other viral infection
Malignancies
Occult abdominal malignancies, especially cancer of the tail of the pancreas
Any other malignancy
Drugs that may cause or aggravate depression
Corticosteroids and ACTH
Oral contraceptives
Reserpine
α-Methyldopa (Aldomet)
Propranolol (Inderal)
Alcohol
Benzodiazepines (e.g., diazepam or chlordiazepoxide)

reluctance in ruling out this possibility), is made, it is helpful to make a further decision as to whether or not the depressive syndrome is associated with a known antecedent or cause such as a medical disease, exogenous toxins (e.g., drugs), or psychological stress such as bereavement. Table 4 presents a partial list of medical conditions that must be ruled out in a depressed patient.

It is because of this frequent association of the depressive syndrome with serious medical diseases that a thorough *medical workup* with physical examination and laboratory tests is a must in the evaluation of a depressed patient. Once depression secondary to a medical condition is established and the underlying disease diagnosed, the depressive syndrome usually abates when the underlying disease has been satisfactorily treated (vignette 4). If a thorough medical evaluation rules out possible underlying disease, then the possibility of primary depression should be entertained.

Depressive syndrome is an integral part of a psychiatric disorder called major *affective disorder* (primary depressive illness, endogenous depression, manic-depressive illness). In this disorder, the symptomatology of the patient is usually severe enough to meet fully the criteria

for diagnosis of the depressive syndrome. In addition, there is often a positive *family history* of depression, mania, suicide, or alcoholism. About 15–20% of the first-degree relatives of patients with major affective disorders have histories of similar illnesses. History of a previous depressive episode is common, since in 95% of patients, one or more episodes of depression can be expected to occur within ten years after the initial episode. The first episode may occur at any age, but is most common in middle age. In some patients, depressive episodes may alternate with, or be associated with, manic episodes (bipolar affective disorder). It appears that the *unipolar* and *bipolar disorders* have different genetic vulnerability, so that a depressed patient who has a relative who had manic episodes may eventually have a manic episode as well.

A depressive episode due to major affective disorder is usually self-limiting, the average duration without treatment being about six to nine months (in bipolar disorder, somewhat shorter; in unipolar, somewhat longer).

Dexamethasone Suppression Test

As previously mentioned, patients with depressive syndrome due to major affective disorder, particularly the unipolar type, tend to secrete high levels of cortisol in the blood, and the dexamethasone suppression test (DST) is often abnormal in such patients. The DST may thus be used to confirm the diagnosis of depressive syndrome (Carroll *et al.*, 1981; Schatzbert *et al.*, 1983).

In an outpatient setting, 1 mg dexamethasone is taken orally at 11 P.M., and blood is drawn at 4 P.M. the following day for cortisol level determination by the radioimmunoassay method. A 4 P.M. cortisol level of 5 μg/dl or above is considered to be a positive result (nonsuppression).

One should be aware that a number of medical conditions, including, of course, Cushing's syndrome, cause nonsuppression in the DST. Simple weight loss may be associated with a positive DST. Many drugs also interfere with the DST. The DST may also be positive in other psychiatric conditions including dementia.

When a depressed patient is successfully treated, the DST seems to revert to normal. Failure of the DST to normalize despite vigorous antidepressant drug therapy may be a poor prognostic sign concerning the depressive syndrome.

As clinical experience accumulates, it appears that the DST may not be as specific as originally thought. Final appraisal of the DST as a clinical diagnostic test awaits further research.

Physical Symptoms in Depressive Syndrome Associated with Major Affective Disorders

Certain physical and physiological symptoms and signs are often present in the depressive syndrome. In fact, some of the physiological signs, such as loss of appetite and weight loss, sleep disturbance, and loss of sexual interest, are part of the diagnostic criteria. In addition, many patients have *vague pains* and *discomfort* in various parts of the body, perhaps associated with a turning inward of attention with depression. To complicate matters even more, some patients who have the depressive syndrome have *primarily* physical symptoms, with relatively mild to moderate depressive affect, and may seek help for physical symptoms such as vague toothaches, headaches, and backaches (related concepts are "depressive equivalents" and "masked depression"). In some, this may be a heterothetic help-seeking behavior (see Chapter 1). In patients complaining of vague physical pains and discomfort whose medical workup is negative, the physician should consider the possibility that the symptoms may be associated with the depressive syndrome. Careful questioning about affect and other associated symptoms and signs and history will usually disclose more features of the depressive syndrome.

EVALUATION OF SUICIDE POTENTIAL

An important consideration in evaluating a depressive patient is the suicide potential. Approximately 15% of depressive patients ultimately commit suicide (Pokorny, 1977). In a study of 134 consecutive suicides, Robins and associates found, on the basis of interviews with relatives and medical records, that about 45% of the suicides probably had a depressive disorder (Robins *et al.*, 1959a, b).

Risk Factors

In a classic book called *Le Suicide* (1897/1966), the French sociologist Emile Durkheim studied the sociological factors influencing suicide rates in different cultural conditions. He found that suicide rates were higher in the Protestant areas of Europe as opposed to the Catholic areas, which he attributed to the spirit of free inquiry and individualism among the Protestants. Durkheim postulated that loosening of the individual's ties with the society, as in the case of Protestants and unmarried persons, tends to lead the individual to question the purpose of life itself and, thus, to a heightened risk of suicide. This type of suicide was called the

"egoistic suicide." Durkheim also described the "altruistic suicide," occurring in an opposite cultural setting. Altruistic suicide occurs in settings of excessive lack of individualism, such as the suicide of women on the death of their husbands in some cultures. In this type of suicide, there is a sense of duty, a social prescription for the suicide. Durkheim also included religious suicides, such as self-immolation occurring in certain Buddhist sects, in the category of altruistic suicide.

Anomie and *anomic suicide* are important concepts proposed by Durkheim. He noted that the suicide rate increased at times of relative peace and financial prosperity. He also noted that the suicide rate was high in the European countries where the divorce rates were high. He postulated that at times of peace, relative financial prosperity, and following divorce and separation, there is a loss of regulation in one's life—that is, the individual feels lost without a sense of purpose and demands. He called this state of lack of regulation "anomie" and the resultant suicide occurring in some individuals "anomic suicide" (Durkheim, 1897/1966).

Current statistics show that suicide is the second leading cause of death for white males between the ages of 10 and 55 in the United States. It is one of the ten leading causes of death for both men and women up to the age of 75. The rate of actually committed suicide is higher for men than for women (3 to 1), but more women than men attempt suicide (2 to 1).

Suicide is common among certain professions, especially physicians. Under the age of 40, suicide is the leading cause of death among physicians, psychiatry leading other medical fields (Schneidman *et al.*, 1975).

In the United States, the rate of suicide in the *general population* is approximately 1 in 10,000. The risk for successful suicide is higher in *single, separated,* or *divorced persons;* in *men;* and in *older persons.* Suicide risk is higher in patients who have pain, who are *depressed,* or who have a history of a depressive syndrome. Patients who live *alone,* who drink *heavily,* and who have experienced a *recent stressful event* are also at a higher risk for suicide.

About 80% of persons who commit suicide give *definite warnings about their intent* (Motto, 1975). Suicides often occur during a phase *when the person's depression seems to be lifting.* When a depressed patient has decided to commit suicide, there may be a sudden lifting of depressive affect, with a sense of resolution (vignette 3). With antidepressant therapy, the suicide risk rises initially as the patient becomes more energetic and able to contemplate the execution of a suicide plan. Many persons intending to commit suicide indicate this decision by such actions as

Table 5. Suicide Risk Factors

1. Presence of a depressive syndrome, including suicidal thoughts; especially, has the patient planned how he would do it?
2. Demographic risk factors: religion (high in non-Catholics), marital status (higher in single, divorced, and separated persons), older age, male sex
3. Presence of a painful condition or other medical disorder
4. Living conditions—living alone increases risk
5. Alcohol use—heavy use increases risk
6. Behavioral warnings of suicide—seeking help (including medical), talking about suicide, giving away possessions, putting personal affairs in order, hoarding drugs, buying weapons, and other similar acts
7. Apparent lifting of depression—suicide occurs more often following this
8. Ready availability of the means of suicide, for example, large quantities of prescribed medication or a rifle hanging in the den
9. Previous suicide attempt, history of depression, family history

making out a will, getting insurance, and giving away personally valued possessions (as in vignette 3).

Many people who ultimately commit suicide have recently *engaged in help-seeking behavior.* (Seventy percent of depressed persons committing suicide were in touch with a physician within 30 days of their death, and nearly half during the preceding week.)

To recap, then, suicide potential should be evaluated by asking specific questions about the risk factors listed in Table 5.

Suicide Attempt

The physician usually encounters the suicidal patient in two contexts: the patient who is depressed and therefore a suicide risk and the patient who comes to the physician's attention because of a suicide attempt. The latter is an especially important problem encountered in emergency rooms and intensive care units.

It used to be said that suicide attempters seldom actually commit suicide—this is *not* true. Approximately 1% of suicide attempters who were admitted to the hospital complete suicide *each year* (Weissman, 1974). Although not all suicide attempters ultimately wind up committing suicide, the suicide attempt is usually an indication of serious suffering, which may be alleviated if proper help is offered by the physician.

In contrast to completed suicides, suicide attempters tend to be *young* (peak age, 20–24 years), 50% of attempters being under 30 years of age (Weissman, 1974). Again, unlike completed suicides, women outnumber men by 2 to 1 among suicide attempters.

Suicide attempt often occurs in the context of *interpersonal difficulties.* Although it is more frequent among separated and divorced persons, suicide attempt also occurs among married persons. Suicide attempt is most frequent among young persons, who also tend to be single. Although, as Durkheim pointed out, suicide mortality is lower in countries that have a large number of Roman Catholics, suicide attempt does not seem to be infrequent among Catholics (Weissman, 1974).

The most common form of suicide attempt is drug overdosage (70–90% of all attempts). Barbiturates, tranquilizers, and antidepressant medications are among the drugs commonly used in suicide attempts.

Evaluation of Suicide Attempt

In evaluating a patient who has attempted suicide, we have to consider (1) the current context, including the immediate reason for the attempt; (2) the recent context or recent events or changes that culminated in the patient's attempt; and (3) the background factors, such as the patient's personality, cultural forces, and the meaning of suicide. (For a detailed discussion of these contexts, see Part III.)

Current Context Factors

Method of suicide attempt. The lethality of the method is an important consideration. A patient who attempts suicide by using a gun is obviously more serious in his attempt than someone who ingests ten tablets of aspirin. However, one has to consider the patient's own ideas about the lethality of the method used. For example, a patient who attempts suicide with aspirin believing it to be very lethal is more serious than someone who takes an overdose of antidepressants believing that antidepressants could not seriously endanger life. (In fact, antidepressants are highly lethal.)

Although ingestion of drugs may not be as *immediately* lethal as shooting, this is still the most common method of suicide attempt and completed suicide. Whether the patient has any *further supply* of the drug (which might be used in a repeat attempt) and *where the drug was obtained* should be ascertained. In one study, over half the patients who committed suicide by overdosage had received prescriptions for fully lethal amounts of hypnotic medication that they ingested, or unlimited prescriptions, from their physicians (Murphy, 1975a). The *physician should be alerted* to the patient's suicide attempt as soon as possible if the patient is brought directly to the hospital.

Emotional state of the patient. This includes the seriousness of *suicidal intent,* presence or absence of *intoxication* or *overwhelming emotion* at the time of the attempt, and degree of impulsivity. The seriousness of the suicidal intent is best evaluated by direct questions of the patient, such as, "What did you have in mind when you took the pills? Did you seriously want to die? What ideas did you have about what would happen after you died?" Alcohol or other drug intoxication, presence of rage, or an impulsive suicide attempt militate against the patient's suicidality being prolonged beyond the current attempt. However, the presence of depressive affect or apathy on a continuing basis indicates continuing suicide risk.

Patient's behavior and psychological state around and after the attempt. If the patient went to a secluded place before ingesting an overdose, the seriousness of the suicide risk should be considered grave, even if the method of attempt was less serious (e.g., aspirin). Making a phone call to a friend after ingestion of an overdose probably indicates the presence of ambivalence and a wish for rescue.

Recent Context Factors: Recent Events, Changes, Stresses

Depression. Eighty percent of suicide attempters are *clinically depressed* (i.e., have the depressive syndrome) at the time of the attempt (Silver *et al.,* 1971). The patients should be *asked specific questions* concerning mood, loss of interest, libido, sleep patterns, appetite, weight loss, fatigue, etc., to determine whether the suicide attempt is a part of the depressive syndrome.

Interpersonal conflict. This includes recent marital problems, arguments with lovers, and separations. In certain situations, the interpersonal conflict may be resolved after a suicide attempt, for example, marital reconciliation. In other situations, no interpersonal change occurs, and the *risk may continue.*

Help-seeking behavior and pain. Suicide attempt occurs often in patients with *chronic or severe pain.* Pain can also be a symptom of a depressive syndrome. Help-seeking behavior of any kind occurs often before a suicide attempt. Understanding the help-seeking behavior pattern of the patient will help the physician to recognize future suicide potential. For example, increased frequency of visits to the doctor with complaints of vague pains may be the most prominent symptom of increasing depression for a patient, culminating in a suicide attempt.

Termination behavior. Persons who have decided on suicide often engage in activities indicating their intention, such as giving away prized possessions and making out a new will (vignette 3).

Previous suicide attempts. Over two thirds of those who eventually commit suicide have histories of suicide attempts or threats (Murphy,

1975b). Positive findings in any of the recent-context factors indicate that the attempt was a serious one requiring thoughtful management.

Background Context Factors: Personality, Constitution, Culture

Demographic data related to the risk factors. The risk for completed suicide increases (if the patient attempts suicide again) with increasing age; in men; in persons whose marital status is single, divorced, or separated; in non-Catholics; and in certain professions (e.g., physicians).

Cultural views on suicide. Culture often influences the desirability of suicide as an option (e.g., in Japanese culture) and the method of suicide. The latter is obviously related to the lethality of the attempt. Culture and early history also often influence the psychological meaning of suicide. For example, death by suicide may mean reunion with a loved one, liberation from pain and suffering, or eternal fire and brimstone.

Personality of the patient. Impulsive personality style tends to increase the risk for impulsive suicide. On the other hand, patients who tend to be orderly and controlling (see Chapter 18) are more likely to be successful in a suicide attempt because of their tendency for careful planning. In the past, "hysterical personality" was considered to have a low risk for actual suicide—this is *not* true. Suicide attempts are very common in hysterical personality, and completed suicide is not uncommon.

Constitutional or genetic factors. These are important in that the depressive syndrome has a genetic predisposition. Family history of suicide increases the risk for the patient's having a major affective disorder and for suicide.

The background context factors provide information on the broad background factors for assessing a patient's suicide risk.

MANAGEMENT OF DEPRESSION

A comprehensive evaluation of the depressed patient is the first step toward management. This includes the nature and severity of the depressive affect as well as the life situation of the patient.

Mild depressive affect occurring in response to loss or separation usually does not require specific treatment. In severe *grief reactions,* a generally supportive environment and empathic attitude by the family, friends, and physician usually allow the "grief work" to proceed to resolution in time. On occasion, the grieving person may be *frightened* about the very vivid images of the deceased that he or she may experience or, occasionally, by *hallucinations* concerning the deceased. Reassurance

by the physician that these are normal phenomena occurring in the course of bereavement or grief is effective and enlightening. Antidepressant medications are generally *not* indicated and are ineffective in uncomplicated grief reactions. If the sleep disturbance is severe or anxiety symptoms are prominent, mild sedatives or tranquilizers may be of transient benefit, for example, 15 mg flurazepam at bedtime for sleep when necessary.

For *chronic depressive disorder,* the recognition of the chronic nature of the depression as a personality style is the key to management. Depressive ways of looking at things, relating with people, and feeling are unlikely to change easily or promptly. The health-care personnel should consider this as a limiting factor in management. Long-term psychotherapy or restructuring of the patient's life may be effective in some instances, but this requires extensive investment of time, money, and effort. When the physiological symptoms and signs of depression are prominent in a chronic depressive disorder, antidepressants may be transiently effective, but the chronic characterological aspects are unlikely to respond.

Once the presence of an *acute depressive syndrome* has been recognized, the physician should determine whether it is due to or associated with a medical disease such as an occult carcinoma or an endocrinopathy. If this is the case, the *underlying medical disease* should be treated. In the meanwhile, if the depressive symptomatology is very severe, including serious suicidal ideations, a *protective psychiatric hospitalization* may be necessary. (The medical disease should be treated in the psychiatric unit, or, if surgery is needed, the patient could be transferred for the operation after initial admission to psychiatry.) Antidepressants are not usually effective in depressive syndromes due to medical diseases.

If the diagnosis of a *major affective disorder* is made in a patient with the depressive syndrome, then specific treatments for this disorder are to be considered.

Before embarking on a specific treatment regimen for the depressed patient, a decision should be made as to whether the patient should be *hospitalized.* If the patient is at high risk for suicide, has active suicidal thoughts or plans, is unable to function at work or home, or cannot care for himself, then hospitalization is definitely indicated.

Psychotherapy as a general measure is valuable and often by itself sufficient in milder cases. Psychotherapy in this context should begin as a supportive relationship with a physician who understands the patient's experience of the illness, who has a hopeful and confident attitude, and who encourages the patient to share and discuss his problems. More ambitious or active psychotherapy with such patients should be under-

taken only by a specialist. The frequency of such psychotherapy can be flexible, but initially it should be at least once a week. If the patient is to be treated as an outpatient, the physician should determine whether the patient needs hospitalization at the time of each therapy visit, as the need may arise in the course of treatment.

In addition to the type of psychotherapy described above, specific treatment for the depressive syndrome that is a part of the major affective disorder may include *antidepressants, lithium carbonate,* or *electroconvulsive therapy.* In patients with bipolar disorder, lithium is helpful in treating the acute manic episode and especially in the prevention of recurring manic episodes. Lithium also has the beneficial effect in unipolar depressions of reducing the frequency and severity of recurrent depressive episodes.

Commonly used antidepressants include the tricyclic antidepressants, the monoamine oxidase inhibitors, and newer antidepressants such as fluoxetine and bupropion. Because the monoamine oxidase inhibitors have many interactions with other medications and certain foods (any food containing tyramine, such as aged cheese, wine, and pickles), tricyclic antidepressants are more commonly used, especially in patients with concurrent medical problems. The use of antidepressants and lithium is described in more detail in Chapter 21.

Electroconvulsive therapy (ECT) is an effective treatment for depression. It is usually performed on hospitalized patients who are very agitated and suicidal. Contrary to popular belief, ECT therapy is quite painless. (The patient is anesthetized with sodium pentothal, and muscles are relaxed with a relaxant such as succinylcholine during ECT.) ECT is a safe procedure. The only absolute contraindication to ECT is increased intracranial pressure or recent cerebrovascular accident.

Generally, *antidepressant medications* should be tried first in conjunction with psychotherapy to treat the depressive syndrome. Antidepressant drugs should be used in adequate doses for an adequate amount of time (at least two to three weeks) before the effectiveness is determined. Since antidepressants are usually potentially lethal medications, however, the prescription for an outpatient should not exceed more than one week's supply (another reason the doctor should see the patient at least every week—to give new prescriptions). If the antidepressant is not effective, or if the patient is acutely suicidal and agitated, the patient may need hospitalization and, possibly, ECT.

With antidepressant therapy or ECT or both, 80–90% of patients with the depressive syndrome will respond dramatically within four to six weeks of treatment. Antidepressant drugs should, however, be continued for at least six to nine months (for the duration of the natural history

of the depressive syndrome, which is about nine months without treatment). For some patients, more intensive long-term psychotherapy for underlying chronic unresolved conflicts that may contribute to depressive episodes may be indicated.

The management of *suicidal states* should also be based on comprehensive evaluation. Depression, intoxication, and other acute psychological and medical states should be managed with specific treatment, protection, and general supportive measures. Acutely suicidal patients should be hospitalized, by commitment if necessary. Long-term management and prevention should be based on each of the factors described in the section on Evaluation of Suicide Potential.

SUMMARY

Sadness is an affect usually associated with loss, failure, or separation. Although sadness and grief are normal experiences, the extreme form, depressive syndrome, is a pathological condition. At the opposite pole from the depressive syndrome in mood is the manic syndrome, also a pathological condition. There are specific features and criteria for the diagnosis of the depressive syndrome.

Affective disorders are the most common psychiatric disorders, affecting approximately 20% of the general population. Unipolar affective disorders are much more common than bipolar affective disorders. Women are affected twice as much as men by unipolar depression, while the sex ratio for bipolar disorder is 1:1.

Grief reaction is a response to acute loss. The symptomatology includes somatic distress, intense preoccupation with the image of the deceased, guilt feelings, irritability, and change in patterns of behavior. The course of bereavement or the grief reaction has been described as consisting of three phases: numbness, pining (anxious searching), and depression and despair. The course of the normal acute grief reaction is approximately four to eight weeks, but a substantial portion of the bereaved continue to feel some distress up to one or two years after the death of a spouse. Pathological grief reactions consist of delayed and distorted grief reactions. Depressive syndrome may also ensue.

Studies of young children separated from their mothers show three phases: protest, despair, and detachment. Phenomena similar to those occurring in the protest and despair phases have also been described in infant monkeys that are separated from their mothers. Monkeys that are

socially isolated from early life also develop difficulties in later life, especially in social and sexual activity.

There is an increased morbidity and mortality due to many causes in depressed patients and in the bereaved population.

Depressive affect may be adaptive. It serves as a signal of a loss or separation. The typical expression and behavior pattern (such a protest or despair) may mobilize social support and nurturance. Reduction of activity and withdrawal may facilitate conservation of energy and resources in the face of adversity. In childhood, the threat of sadness resulting from loss of love and approval by the parents and others may help the socialization and learning process.

The *brain mechanisms* of depression are not completely understood. Presumably, there is a dysfunction of the brain areas involved with pleasurable and unpleasurable affects, including the medial forebrain bundle and the periventricular system, respectively, and perhaps the whole limbic brain. The major neurotransmitters implicated in depression include norepinephrine, serotonin, and acetylcholine. The catecholamine theory of affective disorders postulates that there is an increase in the functional level of norepinephrine in the brain in mania and a decrease in its level in depression. Psychological aspects include possible turning inward of aggression, altered cognitive style due to repeated failures, and the response to the recognition of the inadequacy of the individual to perform a task. An integrated model postulates multiple factors (environmental, psychological, genetic, and neurophysiological) that may lead to a final common pathway of dysfunction in the reinforcement system of the brain.

In depression, there is often a marked increase in the corticosteroids and an abnormal dexamethasone suppression test. Growth hormone response to hypoglycemia is often decreased in depression.

The *evaluation* of depression should consider the severity and nature of depression, suicide risk, advisability of hospitalization, and management plans. *Medical conditions* that may cause depression, such as endocrinopathies and occult malignancies, should be carefully ruled out.

An important consideration in the evaluation of depression is the patient's suicide potential. The risk factors for suicide include male sex; single, separated, or divorced marital status; older age; certain professions; lack of social support; heavy drinking; recent stressful event; anomie; certain religious groups; and, most important, presence of depression and past history of suicide attempt. Among the signs of increasing suicide risk are help-seeking behavior, including contacting a physician for medical problems, seeming lifting of depression, giving away possessions, and reference to suicide.

Suicide attempt is much more common than completed suicide. The uncompleted suicide attempters tend to be younger and female as compared to completed suicides. A suicide attempt often results in the context of interpersonal conflict. It is a serious cry for help and should be evaluated systematically.

The *management of grief reactions* includes supportive interpersonal environment and reassurances concerning the symptomatology when indicated. Antianxiety agents might be indicated transiently in some cases. *Chronic depressive disorder* should be considered a characterological style that is not amenable to rapid change but should be a consideration in managing the patient for concurrent medical problems.

Acute depressive syndrome due to major affective disorder should be treated with psychotherapy (doctor–patient relationship) and a specific treatment such as antidepressant medications or electroconvulsive therapy. In bipolar disorders, lithium carbonate is indicated.

The *underlying medical disease* should be treated in depressive syndrome associated with a medical condition.

An important clinical decision in managing a depressed patient is whether or not to hospitalize. Suicidality and inability to function are indications for hospitalization.

IMPLICATIONS

For the Patient

Depression is often a natural response to a medical illness or hospitalization with attendant loss of autonomy and function. Severe depression (depressive syndrome), however, colors every aspect of the patient's life, including his thinking process (slowed and lacking concentration), outlook (hopeless), and behavior (self-defeating or unable to act). Thus, depressed patients often do *not* consult a physician in the presence of serious symptoms or signs of disease and may have an unrealistically pessimistic outlook on existing disease. On the other hand, a relatively mild depression may increase the tendency for help-seeking behavior, especially when accompanied by vague pains and preoccupation with bodily parts. Depression and bereavement are often contributing factors to disease. Depression increases morbidity and mortality in the presence of medical disease and following surgical procedures.

For the Physician

Since depression is common among medical patients, but often not recognized by the physician (Murphy, 1975b), doctors should deliberately evaluate a patient for possible depression. Since depression can be caused by an underlying, undiagnosed medical disease such as occult carcinoma or endocrinopathies, a thorough medical workup should be performed on a patient who is depressed. When a patient appears mentally slowed or especially apathetic or pessimistic about the medical condition, the possibility of concurrent depressive syndrome should be entertained.

Physicians should also be aware that fatigue, vague pains and aches, insomnia, and somatic preoccupation may be symptoms of the depressive syndrome. In these cases, specific questions should be asked to establish or rule out the presence of the syndrome.

For the Community and the Health-Care System

Since mild depression responds to environmental stimuli, hospitals should provide a cheerful physical and environmental situation for the patients. This may also have a preventive effect. More research by the medical profession is needed to increase our understanding of the mechanisms by which depression and bereavement increase morbidity and mortality.

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