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DEPRESSIVE NEUROSIS

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The Clinical Picture

Depression, one of the major health problems of today, is the most common psychiatric disorder treated in office practice and outpatient clinics. The study of depression is important, not only because of the human misery it causes, but because its by-product, suicide, is a leading cause of death in certain age groups.

Until the past century, depression was described under the label of "melancholia." In the second century a.d., Plutarch vividly described the melancholic as a man who "dares not employ any means of averting or of remedying the evil, lest he be found fighting against the gods." He drives away his friends and physician and "rolls naked in the dirt confessing about this and that sin." Pinel, at the beginning of the nineteenth century, described the symptoms of depression as "taciturnity, a thoughtful pensive air, gloomy suspicions, and a love of solitude."

These accounts are remarkably similar to modern textbook descriptions of depression. The symptoms used to diagnose depression

today are found in the ancient descriptions of disturbed mood, self-blame, self-debasing behavior, wish to die, physical symptoms, and delusions of having committed unforgiveable sin.

There are few psychiatric disorders whose clinical descriptions are so constant throughout history. Because the disturbed feelings are usually a striking manifestation of depression, psychiatrists have generally tended to regard this condition as a "primary mood disorder." This designation is misleading, since there are many components of depression other than emotional deviation, and in some cases depressed patients do not report feeling sad or apathetic.

An inpidual who describes his mood as "depressed" may be referring to normal sadness. On the surface, pathological depression may appear to be an intense, exaggerated form of sadness accompanied by anorexia, insomnia, fatigue, and other symptoms. While depression is regarded by some authorities as a discrete disease entity based on biological disorder, others believe that depression and sadness are two extremes on a continuum of mood reactions.

The key factor in diagnosing depression is *change* in the psychobiological systems— changes involving emotion, motivation, cognition, physiology, and behavior.

A sample of 966 psychiatric patients was studied by the Beck Depression Inventory and semi-structured interviews by experienced psychiatrists to determine the differentiating characteristics of depressed patients. The signs and symptoms listed below occurred from two to ten times more frequently among depressed than non-depressed patients.

Emotional: Sadness or apathy; crying spells; self-dislike; loss of gratification; loss of feelings of affection; loss of sense of humor.

Cognitive: Negative self-concept; negative expectations; exaggerated view of problems; attribution of blame to self.

Motivational: Increased dependency; loss of motivation; avoidance; indecisiveness; suicidal wishes.

Physical and Vegetative: Loss of appetite; sleep disturbance; fatigability; loss of sexual interest.

Emotional changes

The emotional changes which accompany depression must be viewed in the context of the inpidual's premorbid behavior and mood level, as well as what might be considered the "norm" in the patient's age,

sex, and social group. For example, crying spells in a patient who rarely cried before becoming depressed might point to a greater level of depression than it would in a patient who habitually cried even before the depression.

Beck found that 88 percent of severely depressed psychiatric patients versus 23 percent of non-depressed psychiatric patients reported some degree of unhappiness or sadness. Though the dejected mood is sometimes couched in somatic terms, such as a lump in the throat or an empty feeling in the stomach, terms such as “miserable,” “blue,” or “downhearted” are generally used. Of course, inpiduals who are in no way clinically depressed may use these adjectives; the dejected mood may range from feelings of mild, transitory sadness to a profound feeling of hopelessness and worry. The *dysphoric* emotions may also stem from a patient’s feelings about himself; that is, he may feel useless or disappointed in himself.

Loss of gratification, at first involving only a few activities and later encompassing almost everything the patient does, is a distressing feature of depression. Social activities and biological drives are not spared. Saul noted that demands from activities involving responsibility and productivity (for example, college assignments) may upset the “give-get balance.” Initially, the imbalance may be corrected by recreational

activities. In more advanced depressions, however, even passive, regressive activities fail to provide gratification.

Loss of gratification is usually accompanied by reduction of emotional attachments to other people or activities. A decline in the degree of affection for family members may worry a patient and cause him to seek professional help. Some patients have described this feeling as a "wall" between themselves and others. In some cases, love is replaced by apathy or resentment. In an analysis of suicide notes, Bjerg reported that 81 percent of the writers had unfulfilled wishes (other than suicidal).

Depressed women in particular are likely to experience increased periods of crying. Some patients with recurrent depressions mark the onset of depression by a sudden impulse to weep. However, the severely depressed inpidual may find that he cannot cry even though he wants to.

Many depressed patients report that they have lost their sense of humor. Rather than having lost the ability to perceive the "punchline" of a joke, the depressed patient seems instead to have lost the ability to respond emotionally to humor; in short, he does not feel like laughing. Nussbaum and Michaux found that their clinical ratings of improvement of depression correlated well with improvements in the affective

response to riddles and jokes.

Cognitive Changes

Although thought disorders are traditionally associated with schizophrenia and paranoia, recent work has uncovered systematic distortions of reality in depression. These findings may cast doubt on the classification of depression as a primary mood disorder and may also provide clues for the treatment of the disease.

The cognitive manifestations of depression include the patient's distorted views of himself, his world, and his future. I have called this group of thoughts the "cognitive triad." Low self-evaluation, distortions of body image, negative expectations, self-blame, and indecisiveness are characteristic cognitive changes.

Depressed inpiduals view themselves as deficient in qualities that they consider important: popularity, intelligence, physical attractiveness, ability, or financial resources. This sense of personal inadequacy is reflected by complaints of deprivation of love or material possessions. The depressed inpidual finds evidence of his own worthlessness in every experience and feels compelled to blame himself for his faults.

Pessimism and a gloomy outlook on life have been found to

correlate highly with suicidal tendencies. Depressed patients believe that their present state of deprivation is irreversible, and 75 percent of them believe they will never recover. A negative view of the self and the future was found to be highly correlated with depression and dissipated when the depression improved. Engel described the "helplessness-hopelessness" axis in depression—the patient cannot help himself and is unlikely to be helped by outside forces. Wohlford found that depressed patients see the future as highly constricted.

The depressive blames adverse experiences on some deficiency within himself, and then he criticizes himself for having the alleged defect. In the severe state, he may view himself as a criminal or social leper and is prone to blame himself for events that are in no way connected with him. He makes statements such as, "I'm responsible for the violence and suffering in the world."

Vacillation, difficulty in making decisions, and changing decisions are also prominent in the depressive. Several factors contribute to the indecisiveness: (1) the patient anticipates making an incorrect decision, and (2) he would rather evade the situation than go through the mental operations required to make conclusions.

Another cognitive aberration is the patient's distorted image of his

physical appearance. This characteristic is found more frequently in depressed women. The patient regards herself as ugly and repulsive, and she may even expect people to turn away from her in disgust.

Motivational Changes

The typical motivations of the depressed patient are "regressive" in nature. He seeks activities that are the least demanding for him (either in terms of the amount of energy required or the degree of responsibility involved). His wishes to escape may carry him to the point of suicidal wishes, and his desire to shun responsibility may lead him to abandon his family, friends, and vocation.

Another common manifestation of depression is the desire to withdraw from the routine things in life. The depressed person regards his tasks as boring and meaningless and wishes to seek refuge from them; thus, the housewife yearns to leave her daily chores, the clerk longs to get away from his paperwork, the student dreams of faraway places. To the severely depressed inpidual even the most elementary tasks, such as eating or taking medication, seem to be overwhelming. Although he is aware of what he should do, he does not experience any internal stimulus to do it. In short, a "paralysis of the will" sets in.

Increased dependency has also been noted in some depressed

patients, and accentuation of dependency has been assigned a major etiological role in some theories of depression. Dependency, in our sense of the word, refers to the desire for help rather than the process of relying on someone else. Receiving guidance appears to carry special emotional significance and is often gratifying to the depressive.

Physical and Vegetative Changes

Behavioral manifestations in themselves can often lead to a diagnosis of depression.

Most persons who are depressed have sad facial expressions (though some may hide their feelings behind a cheerful mask in "smiling depression"), and women, in particular, tend to weep often. Another characteristic of the depressive is a stooped posture. In retarded depression, movements are slow and calculated, verbal output decreases, and the level of spontaneous actions diminishes. The severe state may even be characterized by stupor or semi-stupor. The agitated patient, on the other hand, is incessantly active and restless. While retardation appears to be a reflection of passivity, agitation seems to be a fight against actual and anticipated torture and pain.

Loss of appetite, which may result in substantial weight loss, loss of sexual responses, and sleep disturbance with early morning wakening,

are also included in the physical and vegetative symptoms of depression. Loss of motivation and escapism seem to be associated with increased fatigue, which correlates highly with lack of gratification and pessimism.

The vegetative symptoms of depression are considered by some writers to be signs of "vital depression" and are viewed as evidence that a biological disorder is the basis of depression.' However, this theory may be erroneous, since the physical symptoms do not correlate well with each other or with the clinical ratings of the depth of depression. Furthermore, the somatic symptoms may be a manifestation rather than a cause of the disorder.

Classification of Affective Forces

In the nomenclature of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-II), involutional melancholia and manic-depressive illness are categorized as "major affective disorders." These two forms of depression are distinguished from the depressive neuroses and psychotic depressive reactions in that they do not seem to be precipitated by life stresses.

The diagnostic label "involutional melancholia" has practically disappeared from recent clinical reports and research, and DSM-II recommends that the diagnosis be given only if other types of affective

illness do not apply. The other “major affective disorder” included in DSM-II is manic-depressive illness, which is subpided into manic, depressed, and circular types. Extreme mood swings, recurrence, and remission characterize the illness. While the manic type consists exclusively of manic episodes with accelerated motor activity and speech, extreme elation, and irritability, the depressed type is marked by mental and motor inhibition. A patient with the circular type of manic-depressive illness may alternate between these two extremes and has experienced at least one manic and one depressive episode.

Perris suggested that bipolar and unipolar depressive psychoses are two separate disorders. Manic and depressive phases characterize the bipolar cases, while the unipolar are marked by depressive episodes only. According to Perris, the two groups differed in terms of age, personality traits, course of illness, response to ECT, flicker threshold, and color-form preference.

Some writers have distinguished types of depression by the way patients react to external events. Gillespie studied several groups of depressed inpiduals and labelled those who responded favorably to environmental influences as “reactive.” The cases which showed no response to encouragement or favorable stimuli were labelled “autonomous.” Another pision is that of agitated vs. retarded depression.

In this case, the disorder is classified according to the predominant activity level.

The unitary school does not believe in a sharp pision between neurotic and psychotic depressions, or between reactive and endogenous depressions. These writers maintain that the distinctions between the two groups are quantitative rather than qualitative in nature.

In the literature, there has been a tendency for psychotic depression to be associated with endogenous depression, while neurotic depression is associated with exogenous (reactive) depression. These distinctions have etiological connotations: endogenous refers to cases caused by some biological disorder, and exogenous refers to those caused by external stress. The former includes involutional melancholia and manic-depressive psychosis, and the latter consists of psychogenic, neurotic, or reactive depressions.

Factor Analyses of Depressive Phenomena

Many investigators believe that the isolation of "types" or subgroups of depression is necessary before the essential nature of affective disorders can be revealed. Some recent research has been directed to the question of whether the symptomatology of depression is unitary in nature, or whether it represents an intricate pattern of related

but mutually exclusive syndromes.

The development of techniques for measuring depression has led to attempts to classify depressive phenomena by factor analysis. After quantitative scores on inpidual test items are intercorrelated and a correlation matrix is prepared, factors are rotated until they are isolated. In some cases, each isolated factor is tested for orthogonality (independence) and ranked according to the magnitude of factor loadings with respect to a particular test instrument. The so-called major factors are given unitary labels which are purported to imply clinical significance.

Several factor analyses of rating scales and depressive symptom inventories have been reported. Hamilton' factor-analyzed his depression scale and extracted six orthogonal factors, the first four of which he called "retarded depression," "agitated depression," "anxiety reaction," and "psychopathic depression."

Grinker et al. studied the intercorrelations of checklists labeled "current behavior" and "feelings and concerns." The data yielded five factors from the feelings and concerns list and ten factors from the current behavior list. When all fifteen factors were combined, four patterns emerged which characterized depression as "retarded empty,"

"anxious," "hypochondriacal," or "angry."

The following orthogonal factors were reported by Overall: (1) depression in mood; (2) guilt; (3) psychomotor retardation; (4) anxiety; (5) subjective experience of impairment in functioning; (6) extreme preoccupation with physical health; and (7) physical reaction to stress.

Another study of depressed patients yielded five orthogonal factors. Friedman et al. described these factors as (1) "classical mood or affective depression with guilt, loss of esteem, doubting, and psychological internalizing;" "retarded, withdrawn, apathetic depression;" (3) "a primarily biological reaction characterized by a loss of appetite, sleep disturbance, constipation, work inhibition and loss of satisfaction;" and (4) "oral demanding depression," which was defined as a "querulous hypochondriacal type."

Two factors were extracted in another factor analysis of a depressive symptoms checklist. Besides a general factor of depression, the authors obtained a bipolar factor that distinguished between endogenous depression and exogenous (neurotic) depression. Carney et al. later extracted a third factor called "paranoid psychotic." The bipolar factor was found to correlate highly with a "general factor of endogenous depression" reported by Rosenthal and Klerman.

In a factor analysis of the Beck Depression Inventory, four patterns were reported: (1) “guilty depression;” (2) “retardation;” “somatic disturbance;” and (4) “tearful depression.”

Other studies’ used the Ward Behavior Rating Scale, the Inventory of Somatic Complaints, and a mood scale which was compiled by the researchers from several sources. Significant correlation clusters, such as “friendliness” and “carefree” were extracted, but seemed to be unrelated to depression. These clusters may indicate that a more well-defined list of factors is isolated with instruments which sample a wider range of behavioral traits.

Paykel classified depressed inpiduals according to a special cluster analysis procedure. The findings indicated a hierarchy of groups. The first level consisted of two groups, one older and more severely depressed, and one younger and more mildly depressed. Subsequent pision of these categories produced four approximate groups. One was characterized by severe illness and corresponded to psychotic depressives as described in the literature. A second group consisted of moderately depressed patients with high neuroticism scores and anxiety. The third group of depressives had a considerable element of hostility, and the last group, comprised of young patients, were mildly depressed with backgrounds of personality disorder.

The factor analytic studies described thus far have dealt with questionnaires, rating scales, and symptom inventories. Weckowicz et al. have attempted to relate the factors obtained from intercorrelation of clinical evaluations, symptoms, and complaints, to measures of psychomotor and physical functions. Patients were administered the Beck Depression Inventory, objective psychomotor tests, the Shagass sedation threshold test, amount of salivation tests, and autonomic nervous system activity tests. Twenty first-order factors and six second-order factors were derived. Of the seven canonical correlations found, the first was a pattern of bodily complaints and somatization, and the second was a pattern of guilt, anxiety, and depressed mood. Two other patterns were indicated, the first consisting of psychomotor retardation with symptoms of atypical depression; the second characterized by psychomotor retardation with disturbance in the autonomic nervous system and typical depression. Two other canonical correlations emerged which suggested depression in an involutional setting with anxiety prominent in one pattern and guilt in the other.

Course and Prognosis

The onset of depression is generally well defined. In most cases, the symptoms progressively increase in severity until they "bottom out" and then steadily improve until the episode is over. While the intervals

between attacks are generally free of depressive symptoms, there is a trend toward recurrence.

Rates of complete recovery from affective disorders range from 80 to 95 percent.' Younger patients have the highest recovery rate—in one study, g2 percent of patients less than thirty years of age recovered, while the rate was 75 percent in the thirty to forty age group.

Studies relevant to the duration of depressive episodes vary, partly because of differences in methodology and diagnostic criteria. Lundquist found a median duration of 6.3 months in patients younger than thirty, and 8.7 months for those older than thirty. He reported no significant difference between men and women in regard to duration. Rennie's results were similar: the first episode lasted an average of 6.5 months. The average duration of hospitalization, according to Rennie, was 2.5 months. Paskind studied non-hospitalized depressives and found the median duration to be three months.

In regard to duration of multiple episodes of depression, earlier studies suggested that there is a tendency toward prolongation of episodes with each successive attack. More recent studies by Paskind and Lundquist however, found no significant increase in duration with recurrences.

Variations relevant to frequency of recurrence among depressives are also reported in the literature. Rennie found that 79 percent of hospitalized depressives subsequently had a relapse. Stenstedt and Lundquist, however, reported respectively, 47 percent and 49 percent incidence of recurrence. Rennie's more stringent diagnostic criteria probably account for his higher percentage of recurrences. In his series, more than half of the depressives had three or more relapses.

Recurrences of depressive episodes may occur after years of apparent good health; Kraepelin reported a recurrence 40 years after recovery from an initial episode of depression. Rennie found that the highest percentage of relapses occurred ten to twenty years following the initial depression. Kraepelin found that with each successive relapse, the symptom-free intervals tended to become shorter. This trend was also observed by Paskind.

Suicide

Depressive episodes may end in suicide; however, the actual risk of suicide among depressed patients is difficult to establish because of problems in determining cause of death. Rennie and Lundquist reported that approximately five percent of patients diagnosed as depressive later committed suicide. A more recent study however, found that 14 percent

of patients diagnosed as psychotic depressive died from suicide.

Pokorny studied the suicide rate among former psychiatric patients in a Texas veterans' hospital. He found the suicide rate for depressed patients to be twenty-five times the expected rate and substantially higher than the rate among patients with other psychiatric disorders. Temoche et al. found that the suicide rate for depressives was about three times higher than that of schizophrenics and alcoholics, and thirty-six times higher than that of the general population. The risk of suicide is greatest during weekend leaves from the hospital and shortly after discharge from the hospital. Temoche et al. reported that half of the suicides they studied occurred within eleven months after discharge.

The best indication of a suicidal risk appears to be the communication of suicidal intent. Thus, the idea that the person who talks about suicide will never carry out his wishes is a fiction. In addition, an unsuccessful suicidal attempt greatly increases the chances of a successful attempt some time in the future.

Measurement of Depression

Rating scales and self-report measures can be extremely useful tools in the research and treatment of depression, especially when one considers the inherent difficulties in obtaining consistent diagnoses. One

such scale, designed to measure the psychological, physiological, and behavioral manifestations of depression, was developed by Beck et al. and factor-analyzed repeatedly. Three studies' reported relatively high correlations between the Depression Inventory and clinicians' ratings of depression. The Depression Inventory discriminated among groups of patients with varying degrees of depression. The scale also reflects changes in the severity of depression following an interval of time.

Similar scales have been reported by Hamilton, Wechsler et al., and Zung. Hamilton's scale has been used for assessing depression in medical inpatients, and for measuring psychiatric inpatients' reactions to antidepressant medications. Another scale by Humphrey is a combination of some of Zung's items and some of his own, which were designed to assess functional disturbances resulting from depression, such as performance at work.

Some instruments which were developed to measure general pathology include items on depression. Examples are the Malamud-Sands Psychiatric Rating Scales, the Minnesota Multiphasic Personality Inventory, the Lorr Multi-Dimensional Scale, and the Wittenborn Scales. These general scales are usually considered inadequate for purposes of research or therapy in the specific area of depression. The MMPI, for example, is based on the old psychiatric nomenclature, and factor

analytic studies reveal that its Depression Scale contains only one heterogeneous factor which is consistent with the clinical concept of depression.

Other instruments, such as the Lubin Scale and the Clyde Mood Scale, are examples of adjective checklists designed to measure depression alone or in combination with other mood states. One advantage of the Lubin Scale is the incorporation of a number of parallel versions.

Psychoanalytic Theories of Depression

The early psychoanalytic view of depression was primarily a description of the interaction between drives and affects, such as feelings of loss, guilt, and orality. In his writings of 1911 and 1916, Abraham postulated that the depressive's capacity for affection is undermined by feelings of hatred and hostility brought about by unsatisfied sexual desires. Unable to love, the depressive's hostility is turned inward by means of reverse projection, i.e., "I am hated because of my defects." He tends to be irritable, seeks revenge, and feels intense guilt. In his later works, Abraham supported Freud's ideas regarding pregenital sexuality, and suggested that the refusal to eat could be explained by the unconscious wish to eat up the love object. To document his thesis,

Abraham described several patients who continued to associate sexual gratification with the act of eating.

Freud's paper of 1917, "Mourning and Melancholia," analyzes depression in analogy to normal grief. While both reactions may be the result of a lost love object, in melancholia the loss occurs within the ego. The depressive's hostility toward the lost love object is manifested in his self-accusations. The ego is identified with the abandoned object and feelings of aggression towards the object cause the melancholic to feel deep guilt. A marked decrease in self-esteem, which distinguishes depression from normal mourning, develops in an attempt to punish the incorporated object. The widely accepted role of "anger-in" in the development of depression is largely an outgrowth of Freud's concept of hostility turned inward.

Abraham expands on some of Freud's formulations and draws upon his concept of the psychosexual stages of development. According to Abraham, the depressive's development is fixed at the oral stage, due to an inherited predisposition to oral eroticism and childhood disappointments in love. In his comparison of manic-depressive psychosis and obsessional neurosis, Abraham noted that the obsessional tries to retain his loved object while the melancholic expels the object which has disappointed him. The depressive may then try to repossess

the lost object orally and sadistically punishes it within him.

Depression is described by Rado as “a great despairing cry for love.” He wrote that the depressive is an inpidual with a precarious self-concept and a narcissistic need for approval. When the love object is lost, the depressive’s first reaction is that of rebellious anger; when the rebellion fails, he tries to recapture his self-esteem through the punishment of the ego by the superego. Because of his aggressive nature, the depressed inpidual believes that he is to blame for his loss; simultaneously, however, he blames the “bad part” of the love object in his ego. The internal conflict between the good and bad parts of the introjected object result in guilt and self-reproach.

Melanie Klein theorized that predisposition to depression is rooted in the mother-child relationship in the first year of life, rather than in a series of traumatic experiences. The weak ego of the deprived infant is susceptible to sadness, helplessness, and frustration (“the depressive position”), and there is a failure to build up a strong self-concept independent of the mother’s affection. Klein also depicted the dependent infant’s unconscious fantasies of sadism.

While Rado described depression as a “cry for love,” Fenichel characterizes depressives as “love addicts,” whose self-esteem is

generated by external supplies. Depression is the attempt to coerce the orally incorporated object to return the supplies upon which self-esteem depends, and also to grant protection, forgiveness, security, and love. Like other psychoanalytic writers, Fenichel views depression in adults as a repetition of the "primal depression" in early childhood experience.

Recent psychoanalytic thinkers de-emphasize the drive theory and concentrate on the ego states. Bibring, for example, emphasized the loss of self-esteem within the ego, and viewed helplessness to achieve goals as the primary characteristic of depression. According to Bibring, the disorder is the "emotional correlate of a partial or complete collapse of the self-esteem of the ego, since it feels unable to live up to its aspirations while they are strongly maintained." The three major areas of aspiration are the wish to be loved and valued, the desire to be strong and secure, and the wish to be loving and good. Depression results when these goals are not realized, and the conflict occurs within the ego rather than between the superego and the ego.

Edith Jacobson's ideas are an outgrowth of Bibring's ego-centered views, with loss of self-esteem as the central feature of depression. She states that self-esteem represents the degree of discrepancy between "ego ideal" and "self-representation." In an attempt to delineate the nature of ego regression in depression, Jacobson theorized that early

disappointment and its concomitant self-reproach occur in the early life of a depressive. The prepsychotic personality is extremely defensive and cannot tolerate disappointment. The depressive responds to hurt with denial; when this and other mechanisms fail, the self withdraws from reality and becomes helpless and childlike.

In his historical picture of psychoanalytic theories of depression, Gaylin traced the emphasis on decreased self-esteem back to Freud's formulation of the lost love object. According to Gaylin, the loss of self-esteem is a loss of self-confidence which occurs with deprivation or disappointment.

Similarly, Engel described the "giving-up-given-up complex," including these characteristics: (1) helplessness or hopelessness—the effects of giving up; (2) depreciated self-image; (3) lack of gratification from roles or relationships; (4) lack of continuity between past, present, and future; and (5) reactivation of memories of previous periods of giving up.

Relevant criticisms have been directed at some of the psychoanalytic theories described above. Mendelson, for example, has pointed to their tendency to incorporate all psychological behavior into a single vast formula, thus overly simplifying a complicated problem. The

formula is often derived from insufficient data, and the emphasis on very early childhood events is a shortcoming. Not enough attention is paid to events in later life, and empirical validation is scanty. Also, rather than using data to arrive at a theory, analysts have been prone to interpret data to support the a priori theory. One hypothesis in psychodynamics, however, has been subject to systematic study; namely, the relation of "object loss" to depression.

Parental Deprivation and Depression

Many authors have commented on the relationship between early parental separation and the subsequent development of depression. This area of research has been characterized by discrepancies among various studies; for example, the inclusion of endogenous or manic-depressive groups may color the findings. In addition, control data are often absent or inadequate since rates of childhood bereavement in the general population may vary widely.

Brown found a significant relationship between parental deprivation (particularly paternal) in childhood and adult depression. Forty-one percent of the depressed adults he studied had lost a parent before the age of fifteen, while the incidence of orphanhood in England's general population was 12 percent. In a control group of 267 medical

patients, the incidence of early orphanhood was 19.6 per cent. However, the use of medical patients as controls in this and other studies has been questioned, since depressive symptoms are quite common in medical inpatients.

In a group of 297 depressed patients studied to determine the relationship of orphanhood to depression, 27 percent of severely depressed patients were found to have lost a parent before age sixteen, while the non-depressed group had an incidence of 12 percent.

Birk compared 331 depressed outpatients with 296 medical patients and found a significantly greater number of orphans among the depressives. Dennehy reported that depressed females had an excess of paternal loss while depressed males had an excess of maternal loss. Since Dennehy, Birk, and Brown used the 1921 British Census as their source of control data, the comparability of their controls to depressed patients has been questioned by Munro.

Parent-child separation does not appear to be a significant factor in endogenous depression: Gay and Tonge report that parental loss is more frequent in psychogenic than in endogenous depression. No comparison was made with normal controls. Hill and Price compared depressives with other psychiatric patients; they report no excess of maternal loss,

but a significant excess in paternal loss.

Munro suggested that parental deprivation could be related to the *severity* of the depression. This finding was also reported by Wilson, Alltop, and Buffaloe.

These positive findings seem impressive, but there have been studies which failed to establish any significant relationship between separation and depression. Pitts et al. found no significant association between psychiatric illness and childhood bereavement; however, problems arise in the interpretation of this study, due to the aforementioned problems of using medical inpatients as control. It would be necessary, in these cases, to control for the presence of depression in non-psychiatric groups.

A systematic comparison of psychiatric diagnoses and parental loss was made by Gregory using MMPI high points and clinical diagnoses. No significant correlation between any diagnostic group and parental loss was established. Negative findings have also been reported by Brill and Liston.

In a study of 152 depressed patients matched with controls, Abraham and Whitlock found no significant difference in childhood loss of one or both parents. The authors claim that it was not the physical loss

of the parent, but rather the poor interaction between child and parent or between both parents that may have caused the depression.

Further research is necessary before the etiological relationship of parental loss in childhood to adult depression can be definitely established.

Life Stress and Depression

Much of the literature on depression has attempted to assess the relationship between life events and depression. While Freud attributed depression to the loss of a loved object, Bibring emphasized the loss of self-esteem in his theory of depression. More recently, other investigators have attempted to define as endogenous those depressions that occur without an actual loss.

Since we have little satisfactory data regarding the incidence of stressful life events in the general population, carefully controlled studies in this area have been scarce. The following three groups of authors have used medical inpatients as control groups: Forrest et al., Hudgens et al., and Morrison et al.

Forrest et al. compared 158 depressives with 58 controls. In the three years prior to hospitalization, depressed patients had an excess of

stress factors. Hudgens and associates compared 40 hospitalized depressives with 40 hospitalized medical controls and found stressful events to be infrequent in the six months preceding onset of illness. Since patients were excluded if their symptoms disappeared in a few days with the removal of stress, a selective definition of depression was used. A later study by the same group of authors also found few differences between the depressed group and the control group. However, these findings may be questioned, due to the fact that life events are frequently associated with other physical illnesses, and depression occurs among medical inpatients.

While the three studies mentioned above used medical controls, Paykel et al. used controls from the general population. On the average, the depressed group reported almost three times as many life stresses in the six months preceding onset of illness as did the controls. Paykel's findings suggest that certain kinds of events on the Holmes and Rahe Social Readjustment Rating Scale, such as increase in arguments with spouse, marital separation, new job, etc., are more likely than others to occur prior to a depressive episode. Exits from the social field preceded clinical depression significantly more frequently than did entrances. Desirable events (marriage, promotion, engagement) were more common in the control group than in the depressives. The familiar psychoanalytic theme of a lost love object, then, is supported by these

findings.

Cognitive Theories of Depression

Depression may be viewed in terms of the activation of three major cognitive patterns that lead the inpidual to see himself, his surroundings, and his future in an idiosyncratic manner. The content of these patterns revolves around the themes of loss and deprivation.

The first component of the "cognitive triad" is the negative view of self: deprived, defective, or defeated. The depressed inpidual regards himself as lacking in gratification, inadequate, or worthless. He believes that he is undesirable and rejects himself because of his alleged defects. The second component is the negative view of experiences. The patient interprets all of his interactions with his environment as representative of deprivation and defeat. Finally, the negative view of the future permeates his ideation. As he looks ahead, the patient sees an indefinite continuation of his present difficulties and a life of unremitting deprivation, frustration, and hardship.

The other phenomena of depression may be considered as consequences of the activation of the negative cognitive patterns. The affective group of depressive symptoms (feeling sad, hopeless, lonely, bored) can be analyzed in terms of these negative concepts. If a patient

simply *thinks* he is being rejected, he will react with the same negative affect that occurs with actual rejection. Similarly, if the inpidual believes he is a social outcast, he will feel lonely.

The motivational changes in depression (paralysis of the will, suicidal wishes, increased dependency, and escapist and avoidance wishes) are also related to cognition. "Paralysis of the will" may be considered as a result of the patient's pessimism and hopelessness; since he expects a negative outcome, he is reluctant to commit himself to a goal or undertaking. Conversely, when he is persuaded that he can succeed at a particular task, he may be stimulated to pursue it.

Avoidance and escapist wishes are also outcomes of the negative expectations. Suicidal wishes are an extreme expression of the desire to escape from what appear to be insoluble problems or an unbearable situation. Since he sees himself as a worthless burden, the depressed patient believes that everyone, including himself, will be better off when he is dead.

Increased dependency may also be attributed to negative concepts. The patient sees himself as inept and undesirable; he tends to overestimate the difficulty of normal tasks in life, and expects things to turn out badly. Under these circumstances, many patients yearn for help

from other persons whom they consider to be strong.

Some of the physical correlates of depression may be related to cognitive patterns. Profound motor inhibition appears to be associated with the negative view of the self. When a patient can be encouraged to initiate an activity, however, the retardation and the subjective sense of fatigue are reduced.

How does an inpidual form the concepts that predispose him to depression? Early in life, a child develops many attitudes about himself and his surroundings. Some of these concepts are realistic and facilitate healthy adjustment, while others deviate from reality and make the inpidual vulnerable to possible psychological disorders.

Since the formation of the three types of concepts central to depression (those regarding the self, the world, and the future) is similar, we can use the example of self-concepts as a model for the other two.

An inpidual's self-concepts are clusters of favorable and unfavorable attitudes derived from his personal experiences, from his identification with significant others, and from the attitudes of others towards him. Once a particular concept is formed, it may influence subsequent judgments. Each negative judgment, for instance, tends to reinforce the negative attitude toward the self. Thus a cycle is set up. If

this negative concept persists, it becomes an enduring structure in the inpidual's cognitive organization.

The vulnerability of the depression-prone inpidual is a result of these enduring negative concepts. Although the schemas may be latent at a given time, they are activated by particular kinds of circumstances and consequently may lead to a full-blown depression. Situations reminiscent of the experience responsible for embedding a negative attitude may trigger a depression. For instance, disruption of a marital situation may light up the idea of an irreversible loss that followed death of a parent in childhood.

Situations that lower a person's self-esteem (such as failing an examination or being fired from a job) are frequent precipitators of depression. Another type of precipitating event involves thwarting of important goals or confrontation with an "insoluble" problem. Depression may also be triggered by a physical abnormality or disease that activates the notion that the patient can never have a happy life.

While any of these circumstances might be painful to the average person, they would not cause a depression, unless the person is particularly sensitive to the situation because of his specific predepressive constellation. While a normal inpidual may experience

such a trauma and be able to maintain interest in other aspects of life, the depression-prone person experiences such a constriction of his cognitive field that he is hit by negative ideas about everything in life. It should be noted that depression is often the result of a series of stressful situations rather than one particular situation.

Depressions, as they occur in the preceding description, are due to *specific stress* situations. However, an inpidual may develop a depression when exposed to a *nonspecific stress* situation of overwhelming proportion, or a series of traumatic events. Depending on the content of the predisposing factors, stress situations may lead to depression or to other pathological reactions, such as paranoid reaction, psychosomatic disorders, etc., or no psychological disorder at all.

To clarify further the relationship between cognition and affect, it is necessary to explore how depressive thinking becomes dominant, and why the patient seems to cling to his painful attitudes, despite the evidence of positive factors in his life.

In conceptualizing any life situation composed of many stimuli, an inpidual extracts certain aspects and combines them into a specific pattern. Different people reach dissimilar conclusions, but a particular inpidual tends to be consistent in his responses to similar types of events.

A cognitive *structure* is a more or less permanent component of the cognitive organization, while a cognitive *process* is transient. The term "schema" has been generally used in the literature on cognition. A schema is used for screening out, differentiating, and coding the stimuli that confront the inpidual. Through the matrix of schemas, he orients himself in relation to space and time, and categorizes and evaluates his experiences. When a person is faced by a particular stimulus, a schema related to the stimulus is activated. The data are molded into cognitions, which are defined as any mental activity with verbal content. A schema may be applied to a small pattern involved in a concrete conceptualization, such as tying a shoelace, or to large patterns, such as self-concepts or prejudice.

Although a schema may be inactive at a given time, it is activated when energized. A specific schema can be energized or de-energized by rapid changes in the environmental inputs. The content of a schema is usually a generalization relating to the inpidual's goals, values, and attitudes. From an analysis of the inpidual's style of structuring different experiences, from his free associations, his daydreams and dreams, and his responses to psychological tests, we may infer the content of a schema.

A depressed patient's ideation is marked by typically depressive

themes. As the depression deepens, his thought content is increasingly saturated with these ideas, even though there may be no logical connection between the actual situation and the interpretation. This cognitive impairment is due to idiosyncratic schemas which assume a dominant role in the thought processes of a depressed inpidual.

The systematic errors which lead to distortion of reality in depressed patients include arbitrary interpretation, selective abstraction, exaggeration, incorrect labeling, and overgeneralization. The orderly matching of stimulus and schema is upset by the intrusion of the overactive idiosyncratic schemas which displace the more appropriate schemas. As the idiosyncratic schemas become more active, they are evoked by stimuli less congruent with them; the reality situation is distorted to fit the schema. The patient loses control over his thinking processes and is unable to energize other more appropriate schemas.

In the milder stages of depressive illness, the patient may be able to view his negative thoughts with objectivity, but in the more severe stages, he finds it difficult to even consider the idea that his interpretations might be erroneous. This loss of objectivity may be explained by the fact that the stronger idiosyncratic schemas tend to interfere with the cognitive structures involved in reality-testing and reasoning.

The activated schemas have a direct relationship to the affective response to a situation. If the content is relevant to being deserted, thwarted, undesirable, or negligent in one's duties, the schemas will produce, respectively, feelings of loneliness, frustration, humiliation, or guilt.

The formulation of a feedback model can provide a more complete explanation of depressive phenomena. This system operates as follows: An unpleasant life situation triggers schemas related to loss, negative expectancies, and self-blame. These schemas produce a stimulation of the affective structures connected to them once they are activated. The activation of the affective structures, in turn, further energizes the schemas to which they are connected. In phenomenological terms, the depressives negative ideation leads to sadness; he labels the sadness as a sign that his life is painful and hopeless. These negative interpretations of the affect further reinforce his negative attitudes. Hence, a vicious cycle is produced.

A cognitive formulation presented by Lichtenberg in 1957 hypothesized that depression is the result of felt hopelessness to achieve one's goals when the inpidual blames himself for the failure. In this case, hope was defined as "the perceived probability of success with respect to goal attainment." Lichtenberg believed that neurotic, agitated, and

retarded depressions were each related to a specific type of goal—an expectancy associated with the particular situation, an expectancy associated with a style of behavior, or an expectancy associated with a generalized goal. In each type of depression, the hopelessness is placed in the context of phenomena such as interpersonal relations, perceptions of secondary gains and losses, time perspective, and perception of personal responsibility.

Cognitive Studies of Depression

Beck and Valin reported that ideas of self-punishment were extremely frequent in the delusions and hallucinations of psychotic depressives. A pilot study by Beck and Hurvich and a more comprehensive study by Beck and Ward revealed higher incidences of "masochistic dreams" in depressed patients than in non-depressed patients. These dreams were identified as those which included themes of thwarting, rejection, punishment, disappointment, injury, personal unattractiveness, etc.

Rather than ascribe these "masochistic dreams" to the Freudian notion of the patient's need to suffer, the conclusion of these studies was that the depressive actually pictured himself as a "loser." He regarded himself as deprived of an important source of gratification and as

defective in certain important attributes. It was also found that early memories, various self-ratings, and responses to pictorial stimuli were pervaded by the concept of loss. A Focused Fantasy Test presented sets of drawings in which one twin has a pleasant experience and the other is a “loser.” Depressed patients identified more frequently with the “loser” twin than did a non-depressed group of patients.

Another study of self-concept in depression was conducted by Laxer," who showed that depressed patients were characterized by low self-esteem and self-blame. Laxer compared depressives with other psychiatric patients; depressives showed a lower self-concept on being admitted to a hospital, but their self-concept improved more at discharge. Plutchik et al. asked manic-depressive patients to describe their ideal self, their least-liked self and their normal self on a forced choice test of emotions. They found that the emotion profile for the depressed state correlated highly with the least-liked self.

One hypothesis derived from the work of Lichtenberg and Beck is that a successful experience will improve certain depressive symptoms such as low mood, pessimism, and low self-esteem. Loeb et ah, for example, devised a study which involved the manipulation of success and failure with a verbal task. After a success experience, the depressed group showed a greater increase in level of aspiration, level of mood, and

expectations of success, as compared with non-depressed subjects. In addition, the depressed group's scores on these indices decreased after failure. In a later study, it was reported that the depressed patients' performance on a subsequent task improved more after success than did the performance of non-depressed subjects.

When a depressed patient believes that he will fail in every undertaking, apathy sets in; thus, cognitive distortions may explain the motivational as well as emotional manifestations of depression. If the depressive sees himself as inept and unable to meet his responsibilities, he may engage in escapism or become overly dependent on others. Loeb et al. found that depressed patients who were led to believe that their performance on a given task was inferior to others were less motivated to volunteer for the experiment again. The lack of motivation may also be related to psychomotor retardation.

The existence of a thinking disorder in depression has been supported by systematic studies. Two such studies demonstrated an impairment of abstract conceptualization, while Neuringer pointed out rigid thinking in depressives. The tendency of depressed inpiduals to think in bipolar opposites (dichotomous thinking) was also reported by Neuringer.'

The concept that the depressed patient has a negative view of the future and low self-esteem was supported by a systematic study. These negative concepts disappeared when the patient recovered from his depression. Melges and Bowlby reported time constriction in depression, and more recently, Melges et al. have reported a high correlation between self-esteem and optimism.

Behavioral Theories of Depression

Behaviorally oriented writers have only recently presented their concepts of depression. Ferster asserted that the loss of a "significant other" causes a sudden reduction in the output of behavior and a decreased rate of positive reinforcement. He also observed the tendency of depressives to restrict the number of persons with whom they interact; this tendency makes the depressed inpidual especially vulnerable to the loss of a loved person or object.

Lazarus proposed that depressions which could not be explained by learning theory principles are probably organic in nature. He viewed depression as a "function of inadequate or insufficient reinforcers." Thus, therapy should help the depressive to take advantage of all available reinforcers or provide a change in the reinforcement schedule. This recommendation is similar to an approach outlined by Burgess; the

therapy is based on the S-R model and has as its goal the extinction of depressive behavior.

According to Patterson and Rosenberry, an inpidual is predisposed to depression if he lacks social skills. Since he has fewer available sources of reinforcement, loss of a source is a greater deprivation for him than for the socially skilled person. In addition, the inpidual lacking in social skills finds it more difficult to replace a lost reinforcer.

Personal characteristics, such as a lack of social skills, or environmental factors may cause the low rate of positive reinforcement, according to a recent study. Testing the hypothesis that depressed inpiduals are lacking in social skills, the authors reported that depressed inpiduals interact with fewer people than do non-depressed inpiduals; depressives also emit shorter messages which are often timed inappropriately. A therapeutic approach was designed by these researchers to positively reinforce constructive behaviors and social skills, while negatively reinforcing depressive behaviors.

Ullmann and Krasner view depression as occurring when previously reinforced behavior no longer results in reinforcement. For example, when a person ages, his role status changes and his rate of positive reinforcement is reduced. The claim that depressive behavior

itself stimulates positive reinforcement in the form of kindness and sympathy is contradictory to the position that depressive behavior alienates other people.

The behavior theorists have been criticized for their neglect of the subjective components of depression, such as sadness, hopelessness, and suicidal wishes. In addition, much of the data used to substantiate various behavioral concepts has been contradictory. In general, behavior theory has been applied only to limited aspects of the phenomena of depression.

Sociological and Demographic Aspects of Depression

Sex

Most studies have shown that depression is approximately twice as frequent in females than in males. Recent studies have revealed that the peak years for women with reactive depression are earlier than those for men and occur prior to menopause. In terms of endogenous depression, Watts found the peak age for women to be concurrent with the menopause, while in men it appears much later.

In a study with medical inpatients, it was found that only slightly more females are depressed and that definite sex-related profiles of

depression emerge. Findings indicated that females tend to somatize, while males refer more often to feelings of personal despair.

One interesting feature of studies which attempt to relate depression and sex is that depression is more common in women, but that suicide is more frequent in men. High morbidity with low mortality in women, and low morbidity with high mortality in men has been observed in other health fields.

Age

Traditionally, depression has been considered an illness of the middle-aged and elderly. It is thought to be rare in infancy and childhood, first appearing clinically in adolescence, reaching its greatest proportions in middle years, and declining to some extent in the later years. In recent years, however, greater attention is being paid to depression in young adults because of a rising suicide rate in persons of this age.

Although depression is thought to occur more frequently in older persons, Redlich and Freedman wrote that depression may be found in all age groups and is not uncommon in young adults. Other studies have found the peak age for reactive depression to be between twenty-six and forty.

The factor of age is important because it may influence the diagnosis of psychotic affective disorders and, thus, the reported age distributions of these conditions. Schizophrenia, for example, is often thought of as a disease afflicting younger persons, while depression is considered an ailment of the middle-aged and elderly.

Race

Stainbrook noted that as far back as 1895 melancholia was relatively uncommon in blacks. In the 1963 fiscal year, reports from all mental hospitals, psychiatric clinics, and psychiatric services of general hospitals in Maryland showed the rates for all mental disorders *except* the affective disorders to be higher among blacks than among white groups.

There have been discrepancies in studies which compare rates of depression in whites and blacks. One found no great racial differences in depressed inpiduals of different races except for the low percentage of blacks with the depressed type of manic-depressive psychosis. Another studied 220 depressed patients in New Haven and found no significant difference in the incidence of depression among blacks and whites, nor in the symptomatology.

Prange compared the incidence of depression among blacks and

whites in the northern and southern United States, and found that southern Negroes have the lowest rates of all the groups. He believes that the incidence of depression in southern blacks will rise as urbanization and the disruption of local cultural patterns occur. McGough et al. studied the changing patterns of mental illness among blacks in the South and predicted a rise in reported frequency of depression as treatment facilities become more accessible to blacks.

Social Class

Class studies of frequency of depression are relatively recent. Hollingshead and Redlich found that the psychotic depressions were two and a half times more frequent in the lower classes than in the upper, while neurotic depressions were twice as common in the upper. The Midtown Manhattan Study of symptom prevalence in the general population reported a consistent inverse correlation between social class and depressive illness.

Marital Status

It is commonly thought that psychiatric disorders occur more frequently among the unmarried. However, most studies show that depression, unlike the other psychiatric illnesses, is more common in married inpiduals. In a study of neurotic depressive women in

psychiatric hospitals, Briggs found that more were married than the general population. Schwab et al. found that depression was almost twice as frequent in the married as compared with the unmarried.

Ethnic Group

It is important to be cautious in interpreting the vast amount of literature on mental illness in peoples of various cultures. Observations in these studies are often impressionistic and misleading because of discrepancies in form and content of mental conditions and also societal attitudes towards psychiatric disorders.

A study of the Hutterites is of particular interest because of the isolation of these colonies and the small degree of intermarriage. The Hutterites are an Anabaptist group with marked religious restrictions who live in the Dakotas and central Canada. The study found that manic-depressive illness was four times as frequent as schizophrenia in these communities. However, this high frequency may be due to inbreeding, which increases the chances of any genetic factors emerging. In addition, prevalence rates decreased significantly when cases active at the time of survey were separated from recovered cases.

Murphy et al. conducted a questionnaire survey of psychiatrists around the world. He concluded that the frequency of depression does

not appear to be related to religion, culture, social class, etc., but rather to the cohesiveness of the community. It must be noted, however, that the methodological shortcomings of this study make it extremely difficult to accept these findings.

Another ethnic study refers to the "air of mild depression that pervades Japanese life" and the high number of suicides in that country, most of which occur between the ages of fifteen and twenty-four.

Depressive disorder was thought to be virtually nonexistent on the African continent until the 1950s. In a review of the literature on the incidence of depression in various parts of Africa, Collomb found incidence rates which varied from 1.1 percent to 15 percent; the discrepancies are due to methodological differences in the studies.

A study of the Yoruba of western Nigeria found many of the symptoms of depression, even though the illness itself was unknown there. In Ghana, comparatively high rates of hospitalized manic-depressives, depressives, non-hospitalized depressives, and attempted suicides have been observed. Depression is also reported to be common in Ethiopia.

Biological Approaches to Depression

Kraines has presented an elaborate theory which stresses the role of biological disorder in the development of depression. He infers that the frequency of depressive attacks in later life, and the occurrence of post-partum and premenstrual depressions are due to hormonal changes. In addition, a physiological basis is suggested because depression may occur in personalities that appear to be well-adjusted. The symptoms, onset, and course of the illness are basically identical in most patients, despite radical differences in culture, status, etc.

Other evidence that seems to confirm the possibility of biological disorder in depression consists in: (1) the beneficial results of physical therapies (ECT and drugs); (2) seasonal peaks of onset in the spring or fall; (3) the precipitation of depression in certain inpiduals by the administration of large doses of phenothiazines.

The role of the hypothalamus is central to Kraines's theory. Depression occurs when the cerebral cortex stimulates the hypothalamus, which in turn excites the somato-visceral system. The feedback from this system is further integrated in the thalamus and limbic system and stimulates the reticular system. The impulses terminate in the cerebral cortex. Kraines believes that mood is derived from this "emotional circuit" and that pathology of the hypothalamus is responsible for manic-depressive illness. Psychopathological symptoms

are secondary in this theory, and are considered to be a defense induced by the physiopathology of the diencephalon.

Kraines's theory, however, is based on fragmentary and questionable evidence. Genetic studies have not clearly delineated the role of heredity in depression; no consistent hormonal abnormalities, except for steroid excretion, have been found; and much of his evidence may also be interpreted to support a psychogenic explanation of depression.

Despite the tremendous amount of research that has attempted to delineate the relationship between depression and biological disorder, there is little solid knowledge of the specific biological correlates of depression. Initial positive results have not been replicated in many cases, and methodological shortcomings often cast doubt on the original findings.

Some studies have been concerned with depression and autonomic function. Funkenstein demonstrated a relationship between depression and blood pressure reactivity by measuring the response in blood pressure to an injection of Mecholyl. However, more precise measures, proper controls, and blind ratings are necessary before these findings can be unequivocally accepted.

Other studies have been conducted to determine whether there is any evidence of a decrease in salivary secretion among depressed inpiduals.'" While most of these findings were positive, longitudinal studies show a discrepancy; once again, better controls are needed to fully interpret the results.

In the area of neurophysiology, one group of studies has attempted to determine the sedation threshold of depressed patients. This work has yielded contradictory data, and no solid evidence has supported the hypothesis that there is a significant difference between the sedation thresholds of neurotic and psychotic depressives.

Electromyograph (EMG) studies measured the muscle action of depressed patients and found that mute and retarded patients show increased muscular activity. In contrast, Rimon et al. found an inverse correlation between muscle tension and severity of depression. Larger samples and control for age are necessary before definite conclusions may be reached.

Studies of the sleep EEG's of depressed patients show that they tend to have excessive periods of light or restless sleep, a shorter period of total sleep, and are more sensitive to noise when asleep. These studies are hampered by the use of normal controls instead of non-depressed

psychiatric patients and the small number of patients used in each study.

Contradictory results have been obtained in studies of the reactivity of the central nervous system in depression. EEG arousal response studies' found an increased threshold for external stimulation during depression and a reduction in the threshold on recovery. Many of these findings have methodological inadequacies, and their findings have been contradicted by one study.

There is some evidence that genetics may predispose an inpidual to depression. By examining the rates of depression among pairs of identical twins, Kallmann found that 22 of 23 twins of patients with manic-depressive illness were also diagnosed as manic-depressive. However, the usefulness of this study is decreased by methodological problems. Slater found a 57 percent concordance rate for fraternal twins, but his sample was even smaller than Kallmann's. Shields compared identical twins reared together with those reared separately. He found that concordance rates for the separated and non-separated twins were the same for cyclothymic features, anxiety traits, emotional lability, and rigidity, though none of his results were significant statistically.

Another technique used to determine the influence of heredity in affective disorder is to assess the incidence of the illness in children of

psychotic parents. Elsasser found that 33 of 47 children of such parents were normal. However, since his cases were drawn from a wide variety of sources, the diagnoses are inconsistent and consequently unreliable.

Family studies have also been used to determine the role of genetics in depression. Stenstedt found a 15 percent incidence of manic-depressive illness in the parents, siblings, and children of 288 manic-depressive patients. The estimated morbidity risk for the general population was 1 percent. Winokur found that alcoholism and affective disorder were significantly more frequent in the first-generation relatives of patients with affective disorder than in a group of controls. Comparing patients whose families had a history of affective illness, Winokur found that almost all of the manic patients belonged to the former group. He also found that daughters of depressed mothers were more likely than sons to be depressed. No such finding occurred in the sons or daughters of depressed fathers.

Biochemical Studies

The study of the biochemistry of depression has been difficult because the tissue of interest—the brain of the depressed inpidual—cannot be chemically examined. Instead, concentrations of compounds active in brain metabolism must be indirectly estimated by measuring

their concentrations in body fluids, usually urine or blood. Many tissues other than the brain contribute to the total concentration of the compounds of interest in body fluids, and thus urine or blood levels do not necessarily offer an accurate index of the amounts of these compounds in the central nervous system.

In general, when a biochemical basis is sought for a particular disorder, it is expected that there will be a single, unique biochemical explanation. In work on the biochemistry of depression, this assumption has tacitly not been made. Studies in the field have not sought (nor found) a "depressed range" for some biochemical parameter in which all inpiduals diagnosed as depressed will score, and in which normal control groups will not score. Rather, these studies have looked for overlapping depressed-normal ranges in which there is nonetheless a statistically significant difference between the two groups for the particular parameter. Such statistically significant differences in overlapping ranges clearly do not offer an immediate possibility for a unique biochemical explanation of depression. However, searching for statistical biochemical differences seems both valid and necessary at this time, given the possible heterogeneity of disorders and diagnostic categories in depression, and the statistical (rather than consistent) effectiveness of antidepressant drugs.

The most extensive work done in recent years on the biochemistry of depression has attempted to test the "catecholamine hypothesis." This hypothesis proposes that in depression there is a depletion of catecholamines (particularly norepinephrine) functioning at adrenergic receptor sites in the brain. In mania, functional brain catecholamine levels are hypothesized to be elevated. The catecholamine hypothesis was originally suggested on the basis of studies of the biochemical effects of antidepressant drugs (MAO inhibitors, tricyclics) in animals. A very considerable amount of data has now been collected on catecholamine levels in humans.

Urinary excretion studies have resulted in a variety of findings. Early studies showed that urinary norepinephrine and epinephrine were lowered in depression. However, Curtis et al. found increased norepinephrine levels in depressed patients (though mainly those with agitated or anxious depressions). Similarly, Bunney et al. found elevated urinary norepinephrine in psychotic but not neurotic depression. Normetanephrine and 3-methoxy-4-hydroxy-phenylglycol (MHPG), two metabolic products of norepinephrine, were shown to be low in the urine of depressed patients and to increase as the depression improved.

Plasma concentrations of catecholamines were measured by a sensitive new technique in a recent study. It presented convincing data

that plasma levels of catecholamines correlated well with anxiety ratings for the patient, but the correlation with depression ratings was not significant. Epinephrine has not been found in the brain of humans, and norepinephrine does not cross the blood-brain barrier in either direction. Thus, the measurement of epinephrine and norepinephrine in the blood or urine probably has little relevance to the catecholamine hypothesis, which states that catecholamines are depleted in the central nervous system. The levels of normetanephrine or MHPG in urine may or may not reflect central nervous system noradrenaline turnover, so these levels (which are decreased in depression) are also of unproved relevance.

Concentrations of noradrenaline have been determined in the *cerebrospinal fluid* by Dencker et al. Their study did not present a statistical treatment of the data, but did show a mean noradrenaline level in depressed patients three times higher than the mean in a control group. (The control group of four subjects was unfortunately small).

Post-mortem examination of the brains of inpiduals committing suicide has been done by two different groups. Both groups found noradrenaline levels in the suicides comparable to those in the same brain areas of control groups that had died of a variety of physical illnesses. Bourne et al. discuss limited reasons to believe that amine

levels have not changed drastically from the moment of death to the time of assay (an average of six months), but neither study presents convincing arguments that body storage, brain removal, freezing, long-term storage, and thawing of brain samples do not significantly alter noradrenaline concentrations.

Precursor administration to depressed patients has been attempted in the thorough study by Goodwin et al. The immediate precursor of brain catecholamines is L-DOPA, an amino acid which can cross the blood-brain barrier. L-DOPA has been successfully used in the treatment of Parkinson's disease, in which dopamine levels are known to be lowered. In the experiments of Goodwin et al. only 4 of 16 depressed patients showed clinical improvement on high doses of L-DOPA, and one of these may have undergone spontaneous remission. The authors suggest that the improvement may have been the result of L-DOPA causing psychomotor activation. They also point out that on the basis of animal studies, even the high dosage of L-DOPA they gave the patients might be expected to change centrally functioning noradrenaline levels only slightly. Dopamine levels would be raised to a greater extent, but in some part the dopamine increase might be localized in capillary walls. Thus, there are also expected weaknesses in this method (precursor load) of examining the catecholamine hypothesis.

In summary, the catecholamine hypothesis is difficult to definitively test. Measurements have been made of catecholamines (and their metabolic products) in blood, urine, cerebrospinal fluid, and stored brain slices. However, the relationship of these measurements to the actual concentration of catecholamines functioning as neurotransmitter in the brain has not been established.

The catecholamine hypothesis has given rise directly to two other important lines of research. The first concerns urinary concentrations of the nucleotide cyclic 3', 5'-adenosine monophosphate (cAMP) in depressed patients. Catecholamines are known in many tissues to activate the enzyme adenyl cyclase which catalyzes the production of cAMP. A recent study has shown that cAMP levels in urine are statistically low in severely depressed patients and high in manic patients. Furthermore, the values return toward normal upon clinical improvement. The same group of authors has also reported that urinary cAMP dramatically rose in seven patients on the day of a switch from depression to mania. They suggest that rapid cAMP elevation may be a “trigger” for a sustained metabolic process responsible for mania. Although these authors claim that physical activity does not significantly affect urinary cAMP concentrations, this point is controversial. Furthermore, it is unknown to what extent urinary cAMP levels reflect central nervous system cAMP levels. Another group has reported normal

cAMP concentration in the cerebrospinal fluid from depressed and manic patients.

Some investigators, considering that imipramine and MAO inhibitors increase other amine levels, have broadened the catecholamine hypothesis to a more general hypothesis, relating depleted transmitter amines of several kinds to depressed mood. In particular, many of the studies examining catecholamine levels have also measured indoleamine concentrations.

In the urine, 5-hydroxyindoleacetic acid (5-HIAA) levels are decreased in agitated depressions, and increased in retarded depressions and in manic conditions. However, much urinary 5-HIAA is known to come from the gastrointestinal tract and diet would be an important factor in these studies.

In cerebrospinal fluid, Dencker et al. and Ashcroft et al. reported a lowered level of 5-HIAA in a depressed group compared to a normal group. However, Ashcroft et al. were very careful in interpreting this difference, noting that a five-fold concentration gradient of 5-HIAA in the CSF made sampling difficult, and effects of physical activity could not be ruled out.

The post-mortem examination of brains of suicides was done for

indoleamines as well as noradrenaline. Pare et al. found that 5-HIAA levels were the same in the brains of the suicides compared to the controls, while there was a slight 5-hydroxytryptamine (5-HT) decrease. They state that the 5-HT decrease is possibly accountable for by suicide-control age differences. Bourne et al. found the opposite; lowered 5-HIAA levels and the same 5-HT levels in the suicide group compared to controls.

It is difficult to reach any strong conclusion on indoleamine metabolism in depression at this time, because of the contradictory findings and the same complexities of interpretation associated with the catecholamine data.

Recent contributions on the role of corticosteroids in depression have been reviewed by Sachar, Coppen and Shopsin and Gershon. The main steroids studied have been limited to 1 x-hydroxycorticosteroids and 17-hydroxycorticosteroids; plasma and urine determinations of their levels in depression and mania have been made. There is controversy surrounding two central points: Are there abnormally high levels of corticosteroids in depression, and does cortisol synthesis in depression respond normally to hypothalamic-pituitary-adrenal feedback as measured by “dexamethasone suppression”? (The steroid analogue dexamethasone when ingested by normal subjects lowers their level of

plasma cortisol measured nine hours later.) Shopsin and Gershon take the position that though many studies have found elevated plasma or urinary corticosteroids in a depressed population compared to normal, this elevation is not large and can probably be attributed to general stress and anxiety suffered by the patients. Stress will also cause short-term elevations in normal subjects. Sachar and Coppen echo the view that elevated corticosteroid levels found in most studies of depression are a nonspecific aspect of the condition related to stress. Shopsin and Gershon found normal dexamethasone suppression of plasma cortisol in depressed patients and are unable to explain why Carrol et al. had found that half the patients in their depressed sample did not show normal dexamethasone suppression.

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