The establishment by treaty of procedures for binding third-party settlement in cases where the ISA or the state withholds permission for research within their respective areas of control is the position most favorable to basic research, and one that none of the competing interest groups at the 1973 conference can effectively oppose. Having claimed that a legitimate distinction exists between basic research and limited exploration, the developed countries cannot object to entrusting this determination, when contested, to a neutral body of experts. Nor can developing countries justify in the name of the common heritage claims to the right to bar from their resource zones research certified by an unbiased third party to be in the common interest.

Freedom for science is no longer a universal right. But access to the oceans for research "intended for the benefit of all mankind" is equally justified under the common heritage doctrine. It would be ironic if the new law of the sea that is being created to make this doctrine a reality were to contain provisions which would impede the understanding of the marine environment on which all nations, rich and poor alike, are going to depend increasingly in the years ahead.

References and Notes

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14. P. M. Fye, personal communication.
15. This proposal was made informally, and, although it generated considerable comment, it was apparently never mentioned in official records. I learned of it from A. E. Maxwell, provost of the Woods Hole Oceanographic Institution and a frequent delegate to the IOC.

16. This article would not have been possible without the help of Robertson P. Dinsmore, Richard L. Haedrich, Herman Franssen, Maureen Franssen, Paul M. Fye, Kaleroy L. Hatzikon, and, above all, P. Sreenivasa Rao, who spent many hours introducing me to the mysteries of international law. This article is Woods Hole Oceanographic Institution Contribution No. 3089.

Depressive Disorders: Toward a Unified Hypothesis

Clinical, experimental, genetic, biochemical, and neurophysiological data are integrated.

Hagop S. Akiskal and William T. McKinney, Jr.

Depressive disorders are perhaps the most distressful, and certainly among the most common, maladies that afflict mankind. Although man has known and experienced melancholic states since antiquity, it is only during the past decade or so that we have begun to develop scientific insights into the basic mechanisms involved.

Unfortunately, the literature on depressive disorders, like that on other psychiatric disorders, is composed of isolated research reports, with few attempts at systematically integrating them (*1*). Different schools of thought utilize dissimilar dialects, thereby hindering communication, while ethical considerations often preclude direct testing of hypotheses in human subjects. Studies are being carried out in an attempt to create experimental animal models of depression—models that would simulate the central features of human depressions. This article reviews these studies, as well as other formulations, both clinical and metapsychological, that derive from different frames of reference. We present evidence that depression in animals is sufficiently analogous to human depression to offer insights into the human condition. A comprehensive hypothesis of depression, incorporating and synthesizing findings from different schools, is proposed.

Depression as a Final Common Pathway

Several models of depression, reflecting diverse theoretical orientations, have been formulated.

1) The "aggression-turned-inward" model, originally proposed by Abraham and later elaborated by Freud, sees depression as hostility turned inward upon the loss of an ambivalently loved person (*2*). Although this is the most widely quoted psychological theory of depression, there is no systematic evidence to substantiate it (*3*). Indeed, this theory does not lend itself easily to empirical verification because it is expressed in metapsychological terms.

2) The "object loss" model, which

Dr. Akiskal is assistant professor of psychiatry, University of Tennessee College of Medicine, 42 North Dunlap St., Memphis 38103, and research psychiatrist, Alcohol and Drug Research Center, Tennessee Psychiatric Hospital and Institute. Dr. McKinney is associate professor of psychiatry, University of Wisconsin School of Medicine, 1300 University Avenue, Madison 53706, and research psychiatrist, University of Wisconsin Primate Laboratory.

also has its roots in psychoanalysis (*4, 5*), views depression as a reaction to the loss of a loved object. Although the loss may involve symbolic possessions, such as one's values, status, and self-esteem (*6*), object loss generally refers to traumatic separation from a loved person—that is, the disruption of an attachment bond.

3) The "reinforcement" model, which utilizes behavioral concepts, postulates that depression is the name given to behaviors that result from the loss of major sources of reinforcement, followed by operant conditioning in the form of attention and sympathy (*7*). Depression is equated with chronic frustration stemming from environmental stresses that are beyond the coping ability of the individual, who views himself as being helpless and finds relief in the rewards of the "sick role."

4) Finally, the "biogenic amine" model, which focuses on biochemical derangements, hypothesizes a state of the central nervous system characterized by depletion of biogenic amines (*8*). These neurotransmitters are concentrated in the areas of the brain that mediate arousal, sleep, appetite, sex drive, and psychomotor activity (*9*), functions impaired in depression.

We examine the interrelations among these models and propose a biological final common pathway for depression. Specifically, we argue that depressive behaviors must be understood as occurring on several levels simultaneously rather than as having a one-to-one, direct relationship with a single chemical event in the brain, and that a multiplicity of genetic, developmental, pharmacological, and interpersonal factors converge in the midbrain and lead to a reversible, functional derangement of the mechanisms of reinforcement. According to our hypothesis, then, object losses, interpersonally induced states of frustration and helplessness, and depletion of biogenic amines ultimately result in impairment of the neurophysiological substrates of reinforcement; this impairment is manifested behaviorally as depressive phenomena.

Heterogeneity in Clinical Depression

Defining and classifying depressive disorders are crucial for research. As Klerman suggests (*10*), some of the confusion in research reports may derive from divergent concepts of what constitutes depressive behaviors and from patient populations that are diagnostically heterogeneous.

Depression has been used to denote a variety of conditions, including (i) a normal mood state—for example, grief; (ii) a symptom synonymous with sadness that is seen in many psychiatric disorders; and (iii) a syndrome characterized by psychomotor retardation or agitation, dejection, hopelessness, self-derogation, suicidal preoccupations, insomnia, loss of appetite (anorexia), and loss of libido. To avoid unnecessary confusion, Whybrow proposes the use of "depression" for mood states, while reserving "melancholia" for the syndrome (*11*). A sustained state of deep dejection (melancholia) is a psychobiological final common pathway; once attained, the state becomes autonomous and assumes the dimensions of illness—that is, morbidity, course, prognosis, and response to pharmacological therapies. It should, therefore, be distinguished from the ubiquitous, transient, and minor changes in affective responses which occur as part of everyday living.

The American Psychiatric Association, in the latest edition (1968) of its diagnostic and statistical manual (*12*), classifies depressions into two broad categories: (i) those characterized by antecedent psychosocial conditions—"neurotic depression" and "psychotic depressive reaction"—that are presumably "reactive" to life events and, therefore, are more or less psychogenic and (ii) "involutional melancholia" and "manic-depressive illness," where "the onset of the mood does not seem to be related directly to a precipitating life experience" (hence "endogenous," or coming from within), with the implication that they are biological in origin.

The major problem with this system of classification is that an etiological index—presence or absence of precipitating psychosocial events—is used in defining disorders whose etiology is largely unknown. Moreover, studies have demonstrated (*13*) that the lack of psychosocial precipitants, thought to be characteristic of the "endogenous" depressive, results from *nonreporting*. The severely depressed patient is too disturbed to appraise fully the psychosocial context within which the illness manifests itself; upon clinical recovery, the frequency and type of stressful events, revealed by careful questioning, are no different from those in the "reactive" group. Depressive phenomena are neither inherently psychosocial nor biological (*1, 14*). As a final common pathway, they are the culmination of processes that can be described in many frames of reference. Our hypothesis is an attempt to build conceptual bridges between these various frames of reference.

Robins and Guze propose a system of classification that would exclude etiological considerations (*15*). The label "secondary depression" refers to depressed patients with a history of a definite psychiatric illness other than affective disorder. Currently, little is known about secondary depression, because there are no large-scale systematic studies of it (*16*). On the other hand, "primary affective illness," which is reserved for patients with no psychiatric disorder other than depression and mania, has received great attention from researchers during the past decade. It has been subdivided into two groups: unipolar affective disease, single or recurrent depressions; and bipolar affective disease, characterized by manic attacks in the subject or in his close biological relatives. Clinical (*17*), genetic (*18*), biochemical (*19*), pharmacological (*20*), and neurophysiological (*21*) differences have been described to further substantiate the unipolar-bipolar dichotomy. For instance, bipolar depressives, as compared with unipolars, are characteristically retarded in psychomotor activity (*22*); have high genetic loading for affective illness, suggesting dominant transmission (*18*); are more likely to have postpartum affective episodes (*23*); will switch to mania upon treatment with sympathomimetic drugs (*19*); and their brain waves (average evoked potentials) exhibit neurophysiological overreaction (augmentation responses) when presented with visual stimuli—these responses can be corrected by administering lithium carbonate (*21*). The bipolar type is clinically manifested in affective episodes only (manias and depressions), and the vulnerability might be transmitted autosomally or by X-linkage (*24*). Unipolar depressions, on the other hand, are clinically heterogeneous and apparently are manifested in forms other than depression, such as alcoholism, as suggested by the work of Winokur *et al.* (*25*); the mode of inheritance is uncertain, with some suggestion that it is polygenic (*18*).

The heterogeneity of depressive disorders encountered in clinical practice can be understood as interactions among biological, psychological, and sociological factors (*26*). In view of

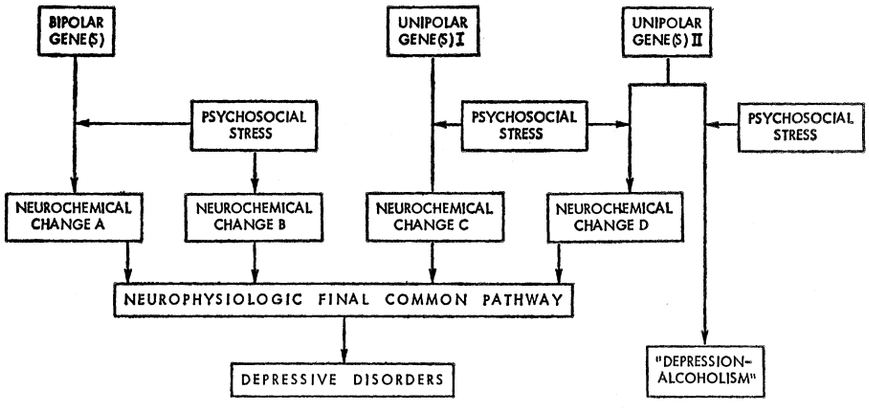


Fig. 1. Hypothetical model of genetic-environmental interaction in depressive disorders.

the evidence for genetic heterogeneity, it is probable that there is more than one biochemical form of depression. On the other hand, little attention has been paid to the possibility that certain forms of depression result from interpersonal factors that secondarily induce biochemical changes in those areas of the brain that modulate affect. Despite the clinical and biological differences described for the various categories of depression (secondary, bipolar, unipolar), many symptoms that constitute the syndrome of depression (psychomotor and vegetative dysfunction, dysphoria, hopelessness, suicidal preoccupation) are common to the entire group of depressive disorders. This uniformity of symptoms is consistent with the hypothesis that a neurophysiological final common pathway underlies all types of depressive illness (see Fig. 1).

Object Loss in Primates

The interaction of genetic and environmental factors in the genesis of human depressions is complex. To study the psychosocial conditions that permit the expression of depressive behaviors in a given individual, who may or may not have a depressive genetic diathesis, one should investigate each of the psychosocial factors. For instance, to state that separation from a loved person might precipitate a depressive condition is not very revealing. One must, for example, specify the age at which separation occurs; the object from whom separation takes place; the nature of the relationship between the two before the separation; the manner in which separation is achieved; and, finally, the length of separation required to cause depression. In other words, one has to define the concept of separation in a system where other factors are kept constant. Obviously this can be achieved most readily at the animal level. Such experimental paradigms would permit rigorous investigation of the behavioral, developmental, and biochemical variables involved. One can do the same with the concept of chronic frustration and helplessness or any other psychosocial factor thought to enter into the pathogenesis of depressive phenomena.

The modeling of certain aspects of the psychopathology of human depressions at the animal level had to await the establishment of objective criteria for the evaluation of nonhuman psychopathology (*27*, *28*) and the production of stable behavioral syndromes. Otherwise, the situation would have been similar to clinical psychiatric research, where confusion in the classification of disorders has often prevented generalization of findings from one study to another.

The nature and variety of reactions to separation have been studied extensively in nonhuman primates because these animals form very strong attachment bonds. These experiments were stimulated by clinical research undertaken by child psychoanalysts.

Spitz (*4*) reported a deprivational reaction in human infants separated from their mothers in the second half of their first year. The reaction was characterized by: (i) apprehension and crying; (ii) withdrawal; (iii) gross retardation of development, retardation of reaction to stimuli, slowness of movement, dejection, and stupor; and (iv) anorexia, weight loss, and insomnia. This syndrome, called anaclitic depression, could, unless reversed by providing a substitute mother, result in death from inanition and superimposed infection. It is interesting that only 15 percent of the infants suffered anaclitic depression. According to Spitz, those infants who had enjoyed a gratifying relationship with their mothers were the ones most susceptible to the trauma of separation. Yet one should also consider the possible interaction of genetic vulnerability with loss of the mother at a critical age.

A similar reaction was described in older children by Robertson and Bowlby (*5*). It had three distinct phases: a "protest" phase, during which the child exhibited restlessness and tearfulness in search for the mother; a "despair" phase, in which the behavior of the child was characterized by apathetic withdrawal; and a final "detachment" phase, in which the child rejected the mother upon reunion.

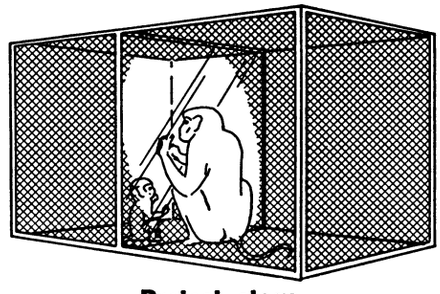
These investigations stimulated research in infrahuman primates, with the purpose of creating animal models of anaclitic depression. Starting in the late 1950's, many experiments were designed at the Wisconsin Primate Laboratory to study the differential effects of maternal separation and social isolation on rhesus monkeys (*Macaca mulatta*) at different ages (*29*). Separation from the mother during infancy provided the best parallel to human anaclitic depression (*30*). Monkeys (5 to 7 months old) that were separated from their mothers but still living with their peers in their original playpen, went through a predictable course of agitation in search for their mothers to almost total lack of interaction with their peers and their environment. This was a rather stable behavioral syndrome, reproduced and amplified by other investigators (*31*). These stages of separation are illustrated in Fig. 2.

In one of the Kaufman-Rosenblum experiments (*32*), four pigtail (*Macaca nemestrina*) infants (4 to 5 months old) that had been reared in a laboratory pen in a group living situation with their feral mothers were separated from their mothers for a period of 4 weeks. The mothers were removed from the original pen, leaving the four infants together. The first 24 to 36 hours were marked by "acute distress" (protest phase): loud screams, searching head movements, pacing, and restlessness. During the next 5 to 6 days, the infants were described as "depressed" (despair phase): they "sat hunched over, almost rolled into a ball," with the head down between the legs, and indulged in self-mouthing; their behavior was generally withdrawn, with

only occasional reference to inanimate objects and almost no interaction with peers.

Anaclitic depression is complicated by the fact that, in addition to the disruption of a strong attachment bond, the loss of the relationship with the mother could markedly interfere with the infant's adaptive responses and, ultimately, survival. Studies of infants separated from their peers (*33*) circumvent this problem, because separation from peers interferes almost exclusively with the attachment bond. The experimental paradigm consisted of either a single, protracted separation or multiple, short separations of a group of four infant macaques that had been reared together since birth. During separation, they went through a protest phase, with excessive vocalization and random locomotion, followed by a despair phase, with marked increase in self-clasping and huddling and marked decrease in locomotion and exploration. One can conclude that the disruption of an attachment bond, whether infant-mother or infant-infant, is a powerful inducer of psychopathology of the "depressive" type.

The age at which separation takes place and prior experience with separation seem to be important factors in determining the form that reactions to separation take. Juvenile monkeys (3 to 4 years old) ordinarily react to separation only with behavior characteristic of the protest phase (*34*). Hence, great caution should be exercised in viewing anaclitic depression as the prototype for adult depressions. On the other hand, a Wisconsin study (*35*) found that juvenile monkeys that had undergone traumatic separation during infancy responded to separation in a manner reminiscent of the despair phase. This suggests that early breaks in attachment bonds could predispose one to adult depression.



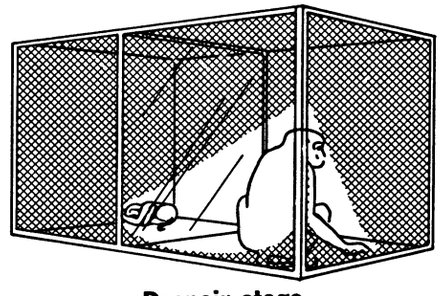


Fig. 2. Illustration of typical protest and despair stages following separation from the mother.

Pharmacological "Depression"

Chemically induced psychopathological states in primates provide further parallels with human depression. Consistent with the biogenic amine hypothesis is the fact that reserpine, a depletor of biogenic amines, precipitates depression in 15 to 20 percent of hypertensive human patients when given in doses of more than 0.5 milligram per day (*36*). In a third of these patients, the depression is serious enough to require psychiatric hospitalization and electroconvulsive therapy. For this reason, the reactions of primates to reserpine have been tested. Rhesus monkeys fed reserpine for 81 days exhibited significant decreases in locomotion and visual exploration and an increase in huddling behavior (*37*). The resemblance to the despair phase of both human and primate infants is apparent (Fig. 3). It would be interesting to compare the effect of reserpine on normally reared adult monkeys with its effect on adult monkeys with a history of traumatic separation. This would more closely parallel the reserpine story in man, since severe depression is induced most readily in persons with a history of depressive illness or a family history of such illness (*36*).

Alpha-methylparatyrosine (AMPT), a selective depletor of dopamine and norepinephrine (*38*), was administered to adult stump-tail monkeys (*Macaca speciosa*) by Redmond *et al.* at the Illinois State Psychiatric Institute (*39*). The animals (which exhibited no signs of toxicity at the end of the study) displayed marked changes in behavior 5 to 6 weeks after treatment with AMPT was begun: (i) decreased total social interactions; (ii) decreased social initiative; (iii) changes in posture and facial expression, suggesting withdrawal and lack of concern with the environment; and (iv) retarded motor activity, without evidence of extrapyramidal reactions. The Wisconsin group found similar results with AMPT (*40*). Both the Illinois (*41*) and Wisconsin (*40*) investigators, however, found no appreciable effects on the behavior of monkeys treated with parachlorphenylalanine, the selective depletor of serotonin (*42*). Monkeys treated with AMPT, despite their "retarded" motor appearance and behavior, exhibited electroencephalographic evidence of arousal. This is consistent with studies in man; contrary to classical notions, evidence for hyperarousal has been found in depressed individuals (*43*).

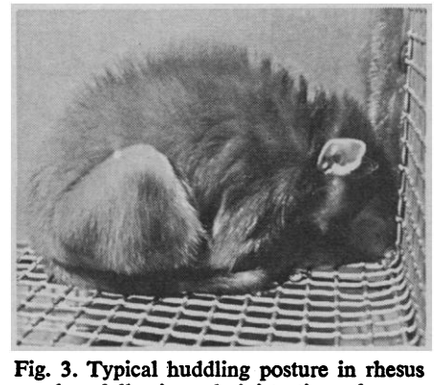


Fig. 3. Typical huddling posture in rhesus monkey following administration of reserpine.

When injected into the central nervous system, 6-hydroxydopamine (6-OHDA) causes permanent destruction of central catecholamine fibers, while leaving the peripheral sympathetic system, and both the central and peripheral serotonergic systems, intact (*44*). Stein and Wise (*45, 46*) have hypothesized that 6-OHDA is somehow involved in the etiology of schizophrenia (and perhaps also of manic-depressive illness). Whether or not this is found to be true, it is now established that 6-OHDA given intraventricularly to rats and rhesus monkeys produces significant changes in behavior. In the adult rat, there is a temporary diminution in activity and in eating and drinking, a reduction in the rate of self-stimulation in the brain, and failure to learn to avoid unpleasant events in active avoidance tasks (*47*). In rhesus monkeys, there is a dramatic decrease in locomotion and social interaction and increased passivity (*48*) (see Fig. 4). These changes in behavior occur after each injection of 6-OHDA; they are temporary, however, despite a permanent depletion of norepinephrine in the brain. This phenomenon requires further investigation, but is generally consistent with the hypothesis presented here. The data from studies of monkeys support the notion that de-

pression is a final common pathway, rather than a specific chemical event, and that it represents the response of the central nervous system to multiple stresses that could be described in interpersonal or biochemical language.

Helplessness and Depression

Is it possible to induce helplessness in animals—that is, a state in which the animal can no longer cope with the frustrations in its environment and simply gives up? For many clinicians, hopelessness and helplessness represent the central feature of human depressions (*49*). For instance, Beck and his associates (*50*) found that "negative cognitive set," the perception of oneself as being helpless and hopeless and having no control over one's fate, correlates best with the depth of depression and suicidal behavior.

"Learned helplessness" is an operational construct which Seligman *et al.* (*51*) use to refer to a stable behavioral pattern characterized by failure to initiate responses to escape traumatic events and failure to learn that one's own responses could be instrumental in terminating noxious stimuli. Dogs were subjected to repeated, inescapable electric shock while strapped in a Pavlovian harness; when these dogs later received electric shock in a shuttlebox, they failed to cross the barrier, thereby "passively" accepting the highly traumatic shock experience. This behavior was in remarkable contrast to that of dogs which had not been previously exposed to inescapable shock; during shuttlebox training, they immediately learned that their response—to jump the barrier—ended the shock. Learned helplessness was reversed by forcibly dragging the dog to the other side of the shuttlebox; apparently the dog learned that its own responses could bring relief from noxious stimulation.

In Seligman's view (*28*), learned helplessness parallels clinical depressions in which the individual loses control over the reinforcers in the environment. Negative expectations about the effectiveness of one's efforts in bringing the environment under one's control (hopelessness, helplessness, powerlessness) lead to passivity and diminished initiation of responses (retardation of psychomotor activity and thought processes, seen clinically).

Such clinical states of helplessness and passivity do not seem to indicate

Fig. 4. Acute behavioral effects following intraventricular administration of 6-hydroxydopamine.

actual deficiencies in the behavioral repertoire of the patients. Some studies have found that depressed patients actively attempt to manipulate their environments (*52*); others have found no evidence of objective deficiencies in actual performance when patients were coerced into engaging in the task at hand (*53*). One is led to conclude that depressed patients have an underlying disorder of motivation and that their ability to derive reinforcement from their environments is impaired.

What interpersonal situations lead to such maladaptive patterns of behavior?

For those in the Wolpian tradition (*54*), chronic aversive stimulation—that is, chronic failure in one's attempts to have the upper hand in interpersonal relationships—culminates in chronic anxiety and inability to reduce anxiety by means of one's usual behavioral repertoire. The clinical picture of such maladaptive behavior, characterized by passivity and hopelessness, is somewhat similar to that of Seligman's dogs. It is claimed that systematic desensitization, aimed at reducing the anxiety, or assertive training, designed to help the individual gain control over interpersonal contingencies, are successful in treating such "neurotic depressions."

Lewinshon *et al.* (*55*), who utilize a Skinnerian frame of reference, state that a low rate of positive reinforcement is the antecedent of depression, which is further maintained by positive reinforcement in the form of sympathy and attention. Lack of "social skill," defined as behaviors that are seldom positively reinforced by others, is viewed as the central behavioral deficit. This concept is useful because it emphasizes the fact that it is not passivity per se which characterizes the depressive, but behaviors that do not reinforce him, no matter how "active" he is. Observations of both the patient and his family at home provide a powerful tool in manipulating interpersonal contingencies that elicit or maintain depressive behaviors. Indeed, managing interpersonal contingencies has proved successful in treating depressed individuals (*56*). Positive reinforcement is provided for active behaviors that take the place of the lost source of reinforcement; such reinforcement, coupled with selective inattention to depressive behaviors, leads to their extinction.

In summary, chronic aversive stimulation, loss of reinforcement, and loss of control over reinforcement are overlapping concepts that describe a state of hopelessness and helplessness deriving from interpersonal relations. A variety of techniques, deriving from both classical and instrumental conditioning, could be utilized to alleviate such depressive states, but apparently these techniques are useful in the milder, so-called neurotic, depressions and that more severe depressions usually require antidepressant drugs or electroconvulsive therapy (*54*). There are two possible explanations for this phenomenon: (i) no matter what interpersonal factors elicit or maintain depressive behaviors, once these behaviors assume severe proportions they become biologically autonomous—the stage of melancholia (*11*)—and, consequently, require somatic therapies; (ii) severe depressions have underlying biochemical predispositions and, therefore, would not respond to any appreciable degree to verbal therapy.

Biogenic Amines and Depression

Disturbances in both classes of biogenic amines, the catecholamines (dopamine and noradrenaline) and the indoleamines (serotonin and tryptamine), have been hypothesized to cause affective disorders (*8*). The catecholamine hypothesis, the first biogenic amine hypothesis to be formulated explicitly, states that depression is associated with a deficiency of catecholamines, particularly norepinephrine, in the central nervous system, and mania with an excess of catecholamine. The possible role of impaired biogenic amine function in these disorders was first inferred from pharmacological evidence (*57*). It was known, for instance, that a syndrome resembling naturally occurring depressions would develop in

hypertensive patients being given large doses of reserpine and alpha-methyldopa over a period of, on the average, 3 months. Both drugs are biogenic amine depletors. It now appears, however, that reserpine is more of a chemical trigger, which upsets a vulnerable biochemical-neurophysiological system, than a primary cause of depression (*36*). As for the pharmacological therapies effective in depression, they are known to raise the level of free amines in the brain (*57*). Tricyclic antidepressants such as imipramine and amitriptyline prevent the reuptake of biogenic amines released from the presynaptic stores, thereby causing a net increase in these transmitters at the postsynaptic junction. Monoamine oxidase inhibitors such as tranylcypromine and phenelzine prevent the oxidative deamination of these amines at the presynaptic stores, again increasing their availability at the receptor sites on the postsynaptic membrane.

Because the effects of reserpine and the antidepressant drugs on biogenic amine metabolism, storage, and release are nonspecific, the pharmacological evidence thus far reviewed does not distinguish between the role of indoleamines and that of catecholamines. Depressed patients have been given the metabolic precursors of these amines in an attempt to discriminate between their respective effects. A collaboration between U.S. and British researchers (*58*) has strengthened the earlier British claims that L-tryptophan, the amino acid precursor of serotonin, has antidepressant properties, especially when coupled with a monoamine oxidase inhibitor (*59*). The catecholamine precursor, L-dopa, on the other hand, has been a failure in therapy, except for a small subgroup of retarded depressives (*60*). The precursor loading strategy, therefore, lends support to the hypothesis that a deficiency of indoleamines in the central nervous system plays an important etiological role in the pathogenesis of depressive disorders (*61*). It also suggests that retarded psychomotor activity, a behavioral correlate of catecholaminergic deficiency in the central nervous system, could be of etiological significance in some depressed patients (*62*). Yet, if optimal states of mood and psychomotor functioning depend on the harmonious functioning of serotonergic and catecholaminergic systems in the diencephalon, then the negative results with L-dopa could perhaps be explained by the decreased serotonin synthesis that has been observed in depressed patients receiving L-dopa (*63*).

Definitive evidence for the biogenic amine hypotheses has to await the demonstration of significant alterations of monoamines in the brains of depressed patients. Although 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, and 5-hydroxytryptamine have been found in low concentrations in the hindbrain of depressive suicides (*64*), one must remember that postmortem neurochemical determinations are beset with methodological problems. However, analysis of the cerebrospinal fluid from depressed patients—and, interestingly, from manic patients—has revealed low concentrations of 5-HIAA (*65*), which, at least in depression, persist with clinical recovery (*61*). Since concentrations of 5-HIAA in cerebrospinal fluid are affected by peripheral (gastrointestinal) sources of indoleamines, the probenecid technique of preventing the active transport of organic acids across the blood-brain barrier has been introduced into clinical research; the results obtained with the probenecid modification, however, have been largely inconclusive, with some suggestion that both dopamine and serotonin metabolites are lowered in concentration (*66*).

As for noradrenaline, about 30 percent of the 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) in the urine is thought to come from the metabolic degradation of noradrenaline in the central nervous system (*67*). This metabolite has been found in subnormal concentrations in depressed patients, returning to normal after treatment with imipramine (*68*). However, it is not clear at present whether low concentrations of MHPG, and low concentrations of metabolites of other biogenic amines correlate best with retarded psychomotor function or with depressed mood (*69*).

In summary, the available data on biogenic amines and depressive disorders do not distinguish between one biogenic amine and another. Although it is possible that distinct groups of depressed patients suffer depletion of a particular biogenic amine, a depletion model based on one biogenic amine is probably an oversimplification. One should perhaps consider the possibility of inefficient interactions of these amines or substitution by faulty neurotransmitters (*70*). The failure of indoleamines to return to normal after the patient's clinical recovery from depression has led to the hypothesis that serotonergic deficiency in the central nervous system determines the patient's predisposition to depressive (and manic) illness; while the depressive episode is triggered by catecholamine depletion (and mania is triggered by an increase in catecholamines). In this view, depression and mania are on a continuum, sharing the same basic dysfunction, rather than being polar opposites, with mania representing a more severe deviation from normal mood (*71*). Bunney, Goodwin, and Murphy have suggested that the available data point to the role of catecholamine excess in exacerbations of manic episodes, but that the underlying dysfunction in both mania and depressions of the bipolar variety probably involves a basic instability of the presynaptic neuronal membrane; such dysfunction is perhaps partially correctable by imipramine or lithium carbonate, or both (*72*). Another hypothesis, postulated by Janowsky, El-Yousef, and Davis, attributes depression to a shift in the balance of norepinephrine and acetylcholine in the diencephalon toward the cholinergic side (*73*). Finally, the work of Prange *et al.* suggests impaired sensitivity of the postsynaptic monoaminergic receptor (*74*), a condition that can be partially corrected by administering thyroid hormone or thyroid-stimulating hormone on top of the tricyclic antidepressant regimen (*75*). This is an important consideration, since synaptic transmission is determined jointly by presynaptic changes in biogenic amines and by postsynaptic receptor sensitivity. With impaired receptor sensitivity present, it is possible that depression could exist with normal or high levels of catecholamines.

Attachment, Reinforcement, and Biogenic Amines

The original psychoanalytic model, paraphrased by Spitz (*4*) and by Robertson and Bowlby (*5*) as a reaction to the loss of the love object, can also be conceived of in terms of disruption of an attachment bond, as suggested by primatologists (*76*).

Learning theorists like Dollard and Miller (*77*) regard the love of the infant for its mother as a learned "secondary dependency drive" derived from the reinforcement of nursing (*78*). However, the Harlows have demonstrated that the affection of the infant for its mother is independent of feeding and that attachment is a powerful

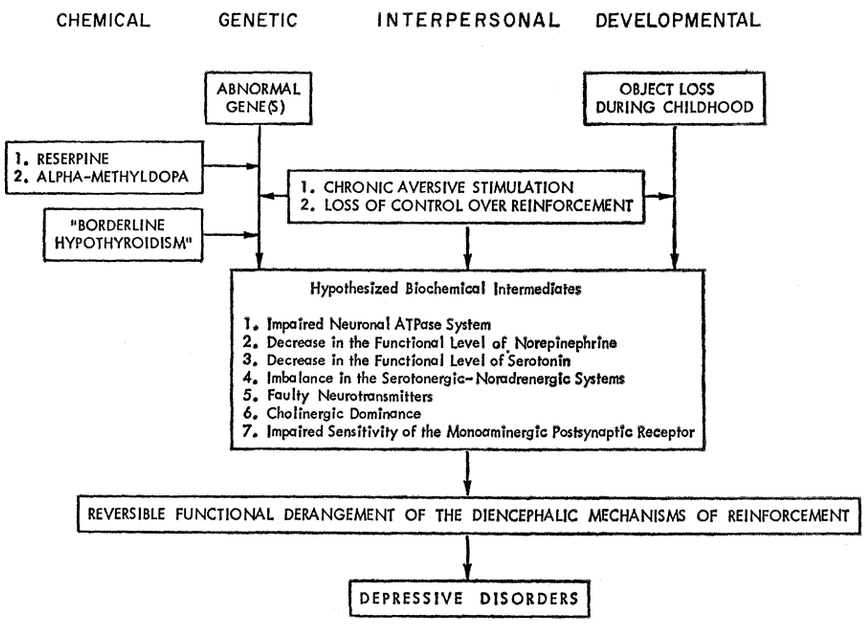


Fig. 5. A multidisciplinary model of the pathogenesis of depressive disorders.

"primary drive" in its own right, just as feeding and sex are (*79*). The attachment of one human being to another, be that infant-mother or peer-peer, is a powerful reinforcer, and its loss can lead to serious psychopathology. This fact gives psychoanalytic, ethological, and behavioral theories a common denominator: depression is associated with the loss of significant reinforcers. Although the behavioral formulation is a broader one, it is a common clinical observation that human depression is usually a reaction to withdrawal of reinforcement from significant others. In primate species, including man, object losses in the form of disrupted attachment bonds are probably the most traumatic examples of loss of reinforcement. Seligman's formulation is even broader, because it views loss of reinforcement as a special instance of loss of control over reinforcement. In conclusion, loss of reinforcement, however achieved, seems to be antecedent to a perception of oneself as having lost one's ability to exercise future control over such reinforcers.

Is it possible to reconcile this behavioral-ethological formulation with the biochemical point of view? Stein's work (*80*) links the pharmacology of depression with the neurophysiological substrates of motivation and reward. Thus amphetamines, euphoriant agents, when injected through permanently implanted electrodes into the "reward centers," increase self-stimulation. Imipramine, an antidepressant, augments the action of amphetamines. Reserpine and AMPT, which are known to precipitate a depression-like syndrome, decrease the action of amphetamines.

Extensive studies of the neurophysiological substrates of reinforcement have elucidated the biology of reward and punishment (*80, 81*). The medial forebrain bundle (MFB), the anatomical substrate for the "reward system," originates in the locus coerulus and the adjacent reticular formation and forms noradrenergic synapses in the lateral hypothalamus, at higher levels in the limbic system, and in the frontal cortex. The periventricular system (PVS), the anatomical substrate for the "punishment system," arising in the dorsomedial region of the midbrain, forms cholinergic synapses in the medial hypothalamus and elsewhere in the limbic system. It appears that noradrenaline exercises inhibitory control over behavior-suppressant cell groups in the forebrain, while acetylcholine facilitates the activity of these nuclei. It should be noted that stimulation of certain portions of the noradrenergic system enhances sexual activity; whereas lesions in this system (for example, in the lateral hypothalamus) produce anorexia. Stimulation of the PVS results in behavioral reactions usually associated with pain, such as jumping, biting, and screaming. Finally, simulation along the punishment and reward pathways is analogous to the action of primary reinforcers, in that neutral stimuli, presented just before stimulation, acquire secondary reinforcing properties.

Thus "one may think of the noradrenergic medial forebrain bundle fibers as part of a behavior-facilitating or 'go' mechanism [that] . . . initiates facilitatory feedback [and] . . . increases the probability that the behavior will run off to completion" (*46*, p. 348). The MFB contains serotonergic fibers too (*82*).

Toward a Unified Hypothesis

From the foregoing information one can predict that impairment of biogenic amine function would result in diminished initiation of responses, decreased activity, and disturbances in appetite, sex drive (*9*), and sleep (*83*). It also provides a conceptual bridge between the behavioral and the biological models of depression. Loss of reinforcement influences the behavior of the organism through its effects on the diencephalic mechanisms of reward and punishment. For instance, conventional reinforcers have no effect on behavior when the anatomical or chemical integrity of the self-stimulation system of the diencephalon is disrupted (*84*).

If depressive behaviors elicited by a variety of mechanisms have as their neurophysiological final common pathway a reversible, functional derangement in the diencephalic mechanisms of reinforcement, as we have hypothesized, then chemical, genetic, developmental, and interpersonal-experiential factors should all impinge on the diencephalic centers of reward, as shown in Fig. 5.

1) *Chemical.* Certain drugs or metabolic disorders can suppress or interfere with the neurotransmitters of this system—for example, reserpine and alpha-methyldopa in man, reserpine and alpha-methylparatyrosine in infrahuman primates; and "borderline hypothyroidism" which could chemically interfere with the sensitivity of the monoaminergic receptor.

2) *Genetic.* These factors must act by means of their effects on the chemistry of reinforcement, because chemistry is the only language into which genes translate their message in controlling organismic function. There is substantial evidence for the contribution of heredity in some, if not all, forms of primary affective illnesses (*18*). However, the specific enzymatic defects that lead to the chemical derangements are unknown. If instability of the neuronal membrane is the underlying dys-

function in affective illness (*72*), then one possible enzymatic defect might be in the mechanism that controls sodium extrusion from the neuron—that is, a derangement in neuronal membrane adenosine triphosphatase. The work of Coppen and his associates provides evidence that there may be, in depression, an accumulation of intraneuronal sodium (*85*). It is also known that an increase in intraneuronal sodium results in extraneuronal leakage of biogenic amines (*86*). This hypothetical chain of events can be summarized as follows: Abnormal gene → (periodic) adenosine triphosphatase deficiency → increased intraneuronal sodium → biogenic amine depletion → derangement of diencephalic mechanisms of reinforcement → failure to respond to reinforcement → depressive behaviors (*87*). As indicated earlier, there are most likely several distinct genetic defects that could lead to various patterns of impairment in the functional level or activity of biogenic amines in the diencephalon. Relative insensitivity of the monoaminergic receptors (*74*), which could be caused by a genetically transmitted, defective structural lipoprotein of the postsynaptic membrane, is another possibility. According to the scheme presented here, and irrespective of the individual lesions, they would all result in a decrease in the functional capacity of the reward system; or a predominance of the punishment system—that is, cholinergic dominance (*73, 80, 82*), to phrase it in neurophysiological terms.

3) *Interpersonal.* The occurrence of anaclitic depression in human and primate infants deprived of or separated from their mothers can be readily understood if one remembers the work of the Harlows, which showed attachment behavior to be a primary drive (*79*). Its neurophysiological substrate probably resides in the diencephalon, as is true of other primary drives. As noted earlier, depressions in human adults are often preceded by the withdrawal of reinforcement from significant others, usually in the form of breaks in attachment bonds. Such a state of affairs could conceivably lead to (reversible) derangements in the diencephalon, which would in turn lead to the dominance of the periventricular punishment system.

But is there any evidence that experiential factors lead to derangements of the biological substrates of reinforcement? Weiss *et al.* (*88*) demonstrated that norepinephrine is depleted in the brain of animals exposed to aversive stimuli beyond their coping ability; these animals also suffered anorexia and weight loss. On the other hand, those animals that could cope with or avoid the aversive stimulus did not exhibit such chemical and somatic derangements. To extrapolate to human beings, interpersonally induced states of helplessness, whether from chronic aversive stimulation or loss of control over reinforcement contingencies, could result in alterations of biogenic amines.

4) *Developmental.* Psychoanalysts claim that bereavement in childhood predisposes one to depression in adulthood. Epidemiological evidence for this hypothesis has been generally negative or inconclusive (*89*). It is possible, however, that if the bereavement occurs at certain critical ages it can predispose to adult depression. Furthermore, a good parental substitute might prevent the adverse effects of childhood bereavement. On the other hand, both childhood bereavement and adult depression might be caused by the same factor (for example, genetic vulnerability to depression), since it has been demonstrated that mortality in bipolar illness, both from suicide and other causes, is very high (*18*). Therefore, one would expect patients from families with bipolar illness to suffer bereavement during childhood and depression during adult life. Future epidemiological work should control for these variables. Primate models of depression may help clarify this issue. In a recent study (*35*), 2-year-old monkeys were shown to respond differently to separation, depending on whether or not they had undergone traumatic separation during infancy; those with a history of separation responded with increased self-directed behaviors and social withdrawal, as compared to control subjects. As to the way in which childhood bereavement operates, in terms of the model presented here, one can hypothesize that early breaks in attachment bonds stunt the maturational potential of the brain mechanisms that subserve reinforcement, making them more vulnerable to adult disappointment and frustration—that is, the individual has a "fragile reward system," one which can be easily upset.

5) *Genetic-interpersonal.* Probably genetic predisposition in the form of a "labile diencephalic reinforcement system" (neuronal membrane instability? impaired sensitivity of monoaminergic receptors?) renders 10 to 15 percent of the population (*18*) extremely vulnerable to the effects of interpersonal conflicts or events that result in a decrease in positive reinforcement. That reinforcing events from the environment converge and interact with the reward centers of the hypothalamus has been demonstrated in infrahuman animals (*84*); and there is no reason to believe that man has two separate systems of reinforcement, or that interpersonally defined reinforcement bypasses the diencephalon.

One might raise the question of why genetic vulnerability to depression most commonly manifests itself in middle age and later. Two possibilities suggest themselves: (i) the stresses of late adulthood are such that they result in substantial decrease in positive reinforcement or loss of control over one's destiny—for example, physical decline, chronic illnesses, retirement, financial troubles, loss of children through marriage, and loss of friends through death; and (ii) if an optimally functioning diencephalic reward system depends on adequate levels of monamine neurotransmitters, then a decrease of such amines with age—which would be expected from the finding that concentrations of the enzyme monoamine oxidase in the brain increase with age (*90*)—might provide another answer to the increased vulnerability of the elderly to depression.

Melancholia (*11*), then, can be looked upon as a psychobiological state that is the final common pathway of processes involving interpersonally induced states of mind in which the individual sees himself as losing control over his fate (hopelessness); increased psychic turmoil; increased neuronal excitability and hyperarousal; disturbance of genetically vulnerable neuronal circuits in the diencephalon; depletion of biogenic amines; impairment of the neurophysiological substrates of reinforcement; further decrements in coping mechanisms; and a vicious cycle of more hopelessness, psychic turmoil, and hyperarousal.

Summary

Our scientific understanding of psychiatric syndromes, including the phenomena of depression, has been hampered because of: (i) the use of metapsychological concepts that are difficult to test; (ii) methodological and linguistic barriers that prevent communication among psychoanalysts, behaviorists, experimental psychologists, and

psychiatrists; and (iii) the reluctance of psychiatrists to accept animal models as possible approximations of certain aspects of human psychopathology.

We have attempted to demonstrate that the animal models simulate some of the central features of clinical depression (for example, helplessness and object loss), thereby allowing one to rigorously investigate them from developmental, behavioral, and biochemical perspectives.

The object loss model, as a concrete version of a metapsychological-psychoanalytic concept, has enabled primatologists to study the disruption of an attachment bond. The behavioral model accommodates this concept to a broader generalization: loss of reinforcement or loss of control over reinforcement. We have reviewed the evidence that these processes involve the diencephalic centers of reward or reinforcement, thereby permitting integration of the psychoanalytical and behavioral formulations with the biochemical hypotheses. Also, we have presented data strongly suggesting that the breaking of an attachment bond in the primate represents significant loss of reinforcement that induces helplessness and disrupts motivated behavior.

Finally, we have argued that the depressive syndrome could be caused by interactions of genetic, chemical, developmental, and interpersonal factors, all of which impinge on the diencephalic centers of reinforcement.

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Computer and Information Networks

The movement in research and education toward national resource sharing via networks is accelerating.

Martin Greenberger, Julius Aronofsky,
James L. McKenney, William F. Massy

A medical researcher sits at an online terminal in Honolulu searching an index to the world's medical literature stored on a computer in Bethesda, Maryland, over 5000 miles away. His request passes across a radio network of the University of Hawaii; the telephone network of the Hawaiian telephone company; the Pacific Ocean via an international satellite; a nationwide research network in the continental United States; and, finally, a commercial time-sharing network, before reaching the medical information system in Bethesda. By mail the request would have taken several days. By computer-communication networks it takes less than 5 seconds. The response to the request, a set of literature citations, starts printing out at the terminal back in Honolulu within 15 seconds from the time the request was dispatched. Numerous other remote users of the medical information system receive service simultaneously.

This example of what is happening now may seem dramatized, but it does illustrate the daily use of a variety of communication networks that are currently providing efficient interconnection between computer systems for their users. Domestic usage of the online medical information system through the commercial time-sharing network has been doubling every 6 months. This fact plus countless other important uses of networks in many areas proclaim the growing significance of information and computer networks. The possibilities they offer in research and education point to new and better computing and information services, greater efficiency in operations, broader markets, widespread access to facilities, and extensive resource sharing.

Responding to the heightened interest in the possibilities of networks, and reflecting its own continuing interest in improving the use of new technologies in research and education (*1*), the National Science Foundation (NSF) in 1972 announced the mounting of "an expanded research program . . . to explore . . . the resource-sharing potential of a national network in support of research and education" (*2*). An NSF grant under this program permitted EDUCOM to bring together interested users and administrators with those possessing shareable resources and relevant experience in a series of three 2-day working seminars. The seminars, held in late 1972 and early 1973, were designed to help identify the central organizational, political, and economic issues in building and operating networks on a national basis.

EDUCOM has been concerned since its founding in 1964 with fostering the collaboration of colleges and universities in the use of computer and communication technologies. It has given the subject of networks special emphasis, beginning with its July 1966 summer study in Boulder, Colorado (*3*), and continuing with the open conferences that it recently has been holding twice each year (*4*). In these working seminars, highly expert technologists joined in discussion with social scientists, physical scientists, decision-makers, and others from many fields (*5*). This article is based on the results of their deliberations (*6*).

This article is adapted from the book *Networks for Research and Education—Sharing Computer and Information Resources Nationwide* (MIT Press, Cambridge, Mass., in press). It reports on a series of working seminars conducted by the authors for EDUCOM with National Science Foundation support. Dr. Greenberger, director of the seminars, is professor of mathematical sciences and senior staff associate of the Center for Metropolitan Planning and Research at Johns Hopkins University, Baltimore, Maryland. Dr. Aronofsky is professor of management science and computing at Southern Methodist University, Dallas, Texas. Dr. McKenney is professor of business administration at Harvard University, Cambridge, Massachusetts. Dr. Massy is vice provost for research and professor of business administration at Stanford University, Stanford, California.