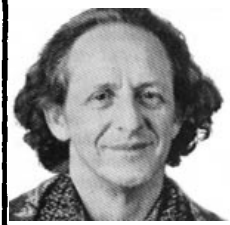

# Current Comments

## What Do We Know about Depression? Part 1: Etiology

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Some time ago, I wrote an essay on the use of electroconvulsive therapy for treating elderly people suffering from severe depression.[1] In dealing with such a specific though widespread manifestation of depression, I only scratched the surface of a much larger problem. Indeed, depending upon your approach to depressive illness, you could easily be left with the notion that you are dealing with a *side effect*, and not a complex *disease*.

Over the past ten years, depression has received much attention in the popular literature. And in fact it has been called "the disease of the seventies." Depression is so widespread that it has been labeled "the common cold of psychopathology."[2] But that very analogy belies the potentially mortal consequences of this illness. Depression is by no means a benign phenomenon like the common cold. While a cold may lead to secondary infections that are occasionally fatal, depression is responsible for up to 70 percent of all suicides.[3] Depression or depressive illness is a serious medical problem that suffers from an identity crisis.

The volume of scholarly books and papers on depression dwarfs the popular literature. It is difficult to be precise because the definition and scope are variable. It is not merely a question of identifying papers that fall under the heading of depression, as we learned when examining our cluster data. Using the names of prominent authors and key words associated with depression, we found 137 clusters over several years in the *Science Citation Index®* (*SCI®*) and the *Social Sciences Citation Index®* (*SSCI™*) data bases. To give you an idea of how far-ranging the field of depression research is, here is a list of some cluster names based on recent *SCI* data: Antidepressant Drugs, Biochemical Classification of Affective Disorders, Biochemistry of Affective Disorders, Cerebral-spinal Fluid in Affective Disorders, Clinical Pharmacology of Tricyclic Antidepressants, Hypothalamic Hormones in Depression, Interaction of Tricyclic Antidepressants and Brain Biogenic-amine, and Lithium Transport Studies in Affective Disorders.

There are a number of psychological and biochemical theories regarding the nature of depressive illness, and all of them have their own implications for therapy. As I found in examining current research on ulcers,[4] the voluminous literature on depression emphasizes both how much is known and how much is yet to be discovered. Moreover, the field of depression research suffers from a terminological problem that dwarfs the "Tower of Babel"[5] in information science education. In formulating their "unified hypothesis" of depression etiology, which I shall discuss, Hagop Akiskal, University of Ten-

nessee, and William McKinney, University of Wisconsin, School of Medicine, complained that "different schools of thought utilize dissimilar dialects, thereby hindering communication."[6] For example, an often used term today is "affective disorder." "Affective" is defined simply as "pertaining to a feeling or mental state."[7] Some authors use affective disorder to describe all depressions. But others use the term "major affective disorder" to describe manic-depression, of which more will be said in this essay, and unipolar depression (manic-depression without mania). They then use the term "minor" or "secondary" affective disorder to describe all other depressions. There are still other ways in which the term affective disorder is used, and this is only one example of how a single term can take on any number of meanings in depression research.

It would be impossible to do a proper review of the multiplicity of viewpoints regarding both the nature and treatment of depression in a single essay. So in this first part, we will examine what the literature says about the causes of depression. Next week, I'll review the diagnosis and treatment of depression. A third essay will focus attention on depression in adolescents. Depression is quite widespread within this age group. While it is a tragic disease at any age, it is doubly tragic that so many young people in the prime of their lives should fall victim to this disease. Suicide is the second leading cause of death among people between the ages of ten and 20 years.[8]

The main symptom of depression is "dysphoric mood," or a subjective feeling of being depressed. This, however, is neither necessary nor sufficient for a clinical diagnosis. In place of dysphoric mood, for example, a patient may present vague somatic complaints, such as headache or backache. In clinical depression, dysphoric mood is accompanied by certain cognitive or perceptual symptoms. The patient may feel low self-esteem, for example, or guilt feelings. Many depressed people find themselves unable to concentrate. Slowed thinking and indecisiveness are common. There may be occasional anxiety, or "panic attacks." Clinicians may observe in depressives certain vegetative signs. Depressed people fatigue easily, for example, and the most simple tasks become too much of an effort. Depressives become passive and lose interest in activities they may have enjoyed before. It is common for them to avoid social contacts and become reclusive. There may be sleep disturbances and changes in body weight.[9]

Most of us feel depressed from time to time. The loss of a job or a loved one might trigger a short-lived depressive episode in just about anyone, with many of the symptoms described above. The question is, does such a "normal" depression differ in kind, or only in degree, from "clinical" depression? Researchers are not sure. Some agree with Sidney Blatt and colleagues at the Yale University School of Medicine, who suggest that depression "can be effectively studied as a continuum from normality through severe clinical disorders."[10] But others, like Akiskal, think that people who suffer clinical depression develop an autonomous disorder that is distinct from "the blues." Mere reassurance or helpful advice from family and friends does not remove the syndrome.[11] Furthermore, in manic-depressives, periods of depression may alternate with periods of hyperactivity and impulsive excitement.

Disagreement over what distinguishes a case of the blues from clinical depression is one reason why it is hard to estimate how many people are afflicted.

Which depressed people do you count? Methodology in collecting data is also a problem.[12] One might count the people who are formally diagnosed as depressed. But what about the people who never present themselves for treatment? It's no wonder that one author describes the literature on the epidemiology of depression as "abundant, contradictory, vague, and confusing."[12]

The picture is further clouded by so-called "masked depressives." Some researchers believe that people may suffer depression without exhibiting the classical symptoms. Instead, these depressives disguise their malaise with alcohol or drug dependence,[13] psychosomatic illnesses,[14] or hypochondria. According to this theory, alcoholism might be viewed as an attempt at self-medication for depression. One practitioner declares, "I have been impressed by the number of alcoholics who successfully stop drinking, only to develop a depressive illness."[12] But the concept of masked depression in adults is by no means universally accepted. "I think that sometimes it is the clinician who is masked," says Akiskal. "If a person has clinical depression, it should generally be possible to validate its presence by other clinical characteristics, even when dysphoric mood is not directly observed."[11]

Despite these problems, attempts have been made to determine how widespread depression is. A 1973 study commissioned by the National Institute of Mental Health concluded that in any given year, 15 percent of all adults may suffer depressive symptoms.[15] Still another source says that in the US and Europe, eight to 11 percent of males and 18 to 23 percent of females have had at least one "major depressive episode."[9] (p. 217) It is well established that more women suffer depression than men. This seems to hold true even after considering such artifacts as a woman being more likely to report symptoms or less likely to mask depression with alcohol abuse.[13] There is no consensus on why more women become depressed. One study found a strong association between marriage and depression in adult women.[16] But this would not explain why females predominate among adolescent depressives also.[17]

Depressive illness has plagued humankind since antiquity. The ancient Greeks attributed it to a preponderance of "black bile," one of the four bodily "humors." This notion persisted until perhaps the sixteenth century. From that time, until early in the twentieth century, a number of explanations for depression were proposed, each reflecting the physiological orthodoxy currently in vogue. It wasn't until the appearance of the psychoanalytic school of thought that depression and other mental disorders were viewed as psychogenic illnesses, something distinct from illnesses of the body.

The psychoanalytic view of depression descends from the separate writings of Karl Abraham and Sigmund Freud early in this century.[18,19] In general, depression is viewed as a complex reaction to loss. The loss may be of a loved one, or the loss may be symbolic in nature. Simply stated, the loss causes grief and anger. Guilt over these feelings, however, causes a person to turn this anger against himself or herself. The idea of depression as aggression-turned-inward was widely held for many years.

But critics of the psychoanalytic view charge that too many of its postulates are untestable. One former practitioner of psychoanalysis complains that Freudian views of depression "are so complex and remote from observables...that they are not readily reduced to operational terms for systematic study."[20] That practitioner is Aaron Beck, now pro-

fessor of psychiatry, University of Pennsylvania, and director of the Center for Cognitive Therapy in Philadelphia. In the mid-1960s, Beck broke with psychoanalysis and formulated the cognitive model of depression, which has since gained wide acceptance.

The cognitive model postulates that depression results from systematic errors in the way a person interprets information received from the environment. Moreover, therapists can observe this process at work in talks with the patient. Cognitive therapists tend to accept patient statements at face value, instead of regarding them as a smoke screen hiding more significant unconscious meanings.

In the cognitive model, the potential depressive has a negative self-image which may have been formed in early childhood. That person then spends a lifetime misinterpreting events in a manner that will confirm and strengthen the negative self-image. For example, if "normal" people receive a low grade in a school subject, they may attribute it to a simple lack of aptitude for that particular subject. The potential depressive, however, will view the low grade as a general confirmation of his or her worthlessness. Even if an outcome isn't negative at all, he or she will seize upon a detail out of context and distort the meaning of it in a manner that confirms the negative self-image. And since that person is "worthless," the future holds nothing but the promise of more frustration and unhappiness. For such people, a trauma that reflects upon self-esteem, such as the loss of a job, can trigger a full-blown depressive episode.[20]

Since the "negative cognitions" responsible for depression may be formed early in life, researchers have tried to identify those life experiences that might predispose one to depression. It has long been supposed that the loss of a parent at an early age might be an etiological factor. A number of experiments with monkeys have shown that outward symptoms of depression can appear in infants by separating them from their mothers.[21] However, studies in human populations, and there have been many, are inconclusive. Some found the loss of a parent in childhood to be a factor in depression, while others have found otherwise.[22]

In 1978, George W. Brown and Tirril Harris, Bedford College, London, published the results of an extensive survey among working-class women in the city of Camberwell.[23] Among other things, they set out to identify cases of depression within the sample population, and to determine what characteristics these women had in common. They found four "vulnerability factors" which predisposed the women to depression in the presence of a "provoking agent." The first and most crucial vulnerability factor was the lack of a confiding relationship with a husband or boyfriend. The other three were: having three or more children under age 14 living at home, the loss of mother before age 11, and unemployment.[23] These findings, however, have not been universally accepted.[24]

Another important view of depression is the one promulgated by behavior therapists. Perhaps the foremost proponent of the behaviorist view is Peter M. Lewinsohn, University of Oregon. According to Lewinsohn, the crucial concept in the etiology of depression is "response-contingent positive reinforcement."[25] Positive reinforcement is a familiar term. If a dog is given food as a reward for barking, it will learn to bark whenever it is hungry.

Generally speaking, a person who does not receive positive reinforcement for his or her endeavors may become depressed. But there is a proviso. The

positive reinforcement that people need must be response contingent, that is, it must depend on the actions of the individual. This may explain why even children of the wealthy become depressed. Although they may be given such positive reinforcers as new cars and trips abroad, it does not help if they feel these things would have been given to them no matter what they did. To put it crudely, positive reinforcement does not contribute to a person's sense of well-being if he or she does not think it was earned. When a person learns that the outcomes of events are not contingent on his or her actions, then that person becomes passive. Depression is thus defined as a diminution of behaviors which results from a lack of response-contingent positive reinforcement.[25]

Similar to the behaviorist view of depression is the learned helplessness model.[26] In 1967, Martin Seligman and S.F. Maier, University of Pennsylvania, subjected dogs to electric shocks which they could not escape. At first, the dogs yelped and jumped about. But in time, they simply lay down and whined softly. These dogs were then placed in a shuttle box, a box-like structure where experiments are performed, where they were again subjected to shocks. This time, the dogs could have easily escaped the shocks by moving to another part of the box. Yet they remained passive and suffered the shocks in silence.[26] Apparently, they had "learned" that they were helpless to affect the outcome of their situation. These experiments led Seligman and his colleagues to conclude that depression "is the belief in one's own helplessness."[2]

Seligman and his colleagues have replicated their experiments on human subjects, although inescapable loud noise and other benign traumas were substituted for electric shocks.[27] But these experiments have been criticized on methodological grounds.[28] More importantly, Vicky Rippere, Institute of Psychiatry, London, questions whether the experiments with dogs have any relevance for humans. Humans differ from animals in important ways. One difference, Rippere observes, is the use of language, which gives humans access to the experiences of others. This would tend to mitigate the learned helplessness of one's own experience.[29]

Despite criticisms, the learned helplessness model has generated much favorable literature. Eileen Nickerson, Boston University, and colleagues see learned helplessness as one reason more women suffer depression than men.[30] "From childhood, females learn many externally-oriented behaviors and attitudes which foster dependency, for example: the need for the approval of others to experience feelings of self-worth; the need to look attractive to others in order to feel attractive; or the need for a love object to complete one's sense of identity.... Women in our society are taught to behave in a manner in which they do not feel in control... but feel dependent on others for control and direction."[30]

For all the differences of emphasis between the cognitive model and the behavioral models of depression, one should not conclude that they represent polarized, feuding camps. Indeed, one is struck by the amount of favorable cross-referencing between the two schools. Behaviorists acknowledge that depressed patients report the subjective feelings of worthlessness and other negative cognitions described by Beck, although they view these cognitions as being a result and not a cause of depression. Many behaviorists even use the Beck Depression Inventory, a diagnostic questionnaire developed by Aaron Beck. (More will be said about diagnosing depression in Part 2 of this essay.)

For their part, cognitive therapists freely borrow some behavior modification techniques in treating depression. Beck has published a paper comparing the two treatment regimens.[31] And Jeffrey Young, a colleague of Beck at the Center for Cognitive Therapy, while characterizing the behaviorist view as "narrow," doubts if it and the cognitive model are mutually exclusive.[32]

So far I've said nothing about the physiology of depression. It has long been suspected, of course, that at least some depressions have biological causes. Until recently, depressive illnesses were dichotomized as either endogenous or exogenous (also called reactive).[33] Endogenous depressions were assumed to be somatic in origin. One distinguishing feature of this type was the apparent absence of psychic stress that triggered the episode. It seemed to arise spontaneously. It was assumed that endogenous depressions tended to be inherited and were amenable to such somatic treatments as drug therapy. Reactive depression, on the other hand, was thought to be psychogenic in nature and resulting from a clearly defined psychic trauma, such as the loss of a loved one. Reactive depression was assumed to be treatable through psychogenic therapies such as psychoanalysis and behavior modification.

However, researchers now consider this classification insufficient. The third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, published by the American Psychiatric Association, has formally dropped the endogenous-reactive dichotomy from its discussion of depressive illness.[9] It is now recognized that depression is a heterogenous group of disorders, and to say that one is depressed is no more specific than saying that one has a fever. And it is clear that at least some depressions are somatic in origin, and can be genetically transmitted.[34] In particular, the very specific responsiveness of manic-depressives to lithium therapy speaks strongly for physiological mechanisms, at least in that important subgroup of depression.

Perhaps the most celebrated physiological model of depression is the catecholamine hypothesis,[35] attributed to Joseph Schildkraut, Harvard University. The catecholamines are a group of chemicals instrumental in the transmission of nerve impulses from nerve cell to nerve cell. According to the hypothesis, an insufficient quantity of catecholamine, specifically norepinephrine, produces depression. The presence of too much norepinephrine produces mania, or flights of impulsive excitement. The sharp fluctuations in the levels of norepinephrine that were thought to induce manic-depressive illness were attributed to metabolic failures. But some researchers now think that it's not the *amount* of catecholamines that is responsible for depression. Rather, the work of Fredoline Sulser, Vanderbilt University, suggests that postsynaptic membranes are unable to regulate their sensitivity to catecholamines.[36]

There are other hypotheses. One is that a low level of serotonin in the cerebrospinal fluid characterizes one form of depression.[37] Another states that a deficiency of folic acid, one of the B vitamins, can produce depression.[38] Still another links hypothalamic hormone disorders with depression.[39,40] Given the heterogeneity of depression, it may well be that all of these hypotheses are true for specific types. But the biochemical etiology of depression is still not known for sure. A cautionary note which appeared in *Lancet* three years ago still seems relevant: "Though there have been many apparent breakthroughs, time and again

they have been like elephants' footprints in the mud, making a large initial impression but quickly fading into the background."[41]

Trying to make sense out of the depression literature is not easy because those who favor psychogenic models of depression, and those who favor biochemical explanations, seem not to hear each other. They scarcely acknowledge each other's existence. Very few biochemistry oriented papers even mention possible psychogenic factors in depression. And the reverse is often true.

In the mid-1970s, Akiskal and McKinney made a rare attempt to bridge the gap between psychology and physiology. They reviewed what was known about the psychological and somatic etiology of depression, and attempted to integrate this knowledge into a unified hypothesis.[6,42]

Akiskal and McKinney adopted the term "melancholia," which is again in vogue among researchers, to distinguish a true affective disorder from an isolated case of the blues. With its literal meaning of "black bile," melancholia implies that true depression, no matter what its causes, always expresses itself as a neurophysiological disorder of some sort. Akiskal and McKinney view melancholia as an interaction between interlocking psychological and chemical processes. The site of this interaction in the brain is the diencephalon. One example of how this interaction might work is that a loss of positive reinforcement affects diencephaletic mechanisms resulting in melancholia in a person who is perhaps genetically predisposed. Conversely, if there is a prior disruption in the diencephalon, positive reinforcements will have no beneficial effect. In other words, psychic processes can affect physiology and vice versa. These processes can interact in a number of ways, so that it is pointless to ask whether the psychological disorder or the physiological disorder came first.[6,42]

The work by Akiskal and McKinney has been widely acknowledged in the literature. Yet further attempts to reconcile the knowledge generated by the psychogenic and biochemical schools have been sparse. One hopeful development has been the appearance in 1979 of a new journal, the *Journal of Affective Disorders*, which accepts depression research from all disciplines. As the editors-in-chief E.S. Paykel and George Winokur wrote in the first issue: "Research in affective disorders spans a very wide range of approaches.... These have tended in the past to appear in different journals, and it is not easy for any reader to keep up with them. Now it seems appropriate...to formulate a new journal to bring them together."[43] The *Journal of Affective Disorders*, published by Elsevier/North Holland, is covered in *Current Contents®/Life Sciences*.

Part 2 of this essay will discuss diagnosis and various therapy strategies now in use to treat depression.

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