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EDITORIAL

Conceptualizing depression

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Depression remains a mystery even though one of its manifestations, melancholia (black bile), is the only word that survived intact from the Hippocratic classification of disease to describe a contemporary disorder. While it is understandable that we still do not know what causes depression, it is somewhat more frustrating that we do not know exactly what depression is.

We find it useful to conceptualize depression as a group of central nervous system (CNS) disorders that share a final common presentation characterized by decrements in mood and in the motivation to pursue pleasurable activities. Those disorders include conditions such as endocrine dysfunction, loss-related syndromes, genetic disorders, adverse drug reactions, and organic brain damage due to ischemia. The current classification systems are purely descriptive, but have certain advantages because value judgments are not made. On the other hand, arbitrary criteria can lead to misleading conclusions. Some real examples are offered for the sake of illustration. A middle-aged woman presents as a healthy volunteer for a research study on depression. A structured clinical interview for DSM-IV (SCID) reveals the following history: When in college, over 20 years before the interview, the subject caught her fiancée, whom she thought she would marry, kissing her best friend. She breaks up with the young man, stays in her room devastated, cries all the time, feels sad, has no interest in things that used to interest her, cannot concentrate, loses appetite and weight, has insomnia, and feels guilty. This lasted a little over 2 weeks. Three weeks after this constellation of symptoms started, she returned to her baseline. She soon finds another young man who eventually proposes to her. They get married and have children. The subject has no other episodes of 'depression'. According to current diagnostic criteria the episode described fits criteria for major depression and the person consequently has a lifetime diagnosis of depression. A key question in this case is 'Does she really have depression?'

In contrast, a young woman whose mother, maternal grandmother, maternal aunt, and sister have a diagnosis of depression and take antidepressants, presents with an episode that lasted 9 days of decreased mood, sadness, crying spells, decreased attention, decreased concentration, fatigue, and passive suicidal ideation. According to DSM-IV, because of the duration of less than 2 weeks, she is not depressed. However, in the light of the genetic load and the severe symptoms in the absence of a precipitating stress, aren't these symptoms in reality a manifestation of major depression?

Does someone who presents depressive symptomatology after a stroke have the same disease as someone who is only depressed in the postpartum period? Does someone who presents with depression during treatment with propranolol for hypertension have the same disease as a person who feels depressed in the context of subclinical hypothyroidism? The answer to these questions is 'no', and that is why we endorse conceptualizing depression as a group of diseases with common clinical symptoms.

Two articles in this issue exemplify the heterogeneity of depression. Zubenko *et al* (pages 460–467) identify the genetic susceptibility locus D2S2944 as a risk factor in women (and not men) with recurrent, early-onset depression, a strongly familial condition. This is an interesting finding, which according to the authors 'suggest that there may be important clinical differences in the molecular basis of clinical depression in men and women, or sex-specific differences in the molecular mechanisms that determine resistance to depressive stimuli'.

The article by Capuron *et al* (pages 468–473) shows an association between decreased serum tryptophan levels and depressive symptoms during cytokine treatment of cancer. Cytokines such as interferon alpha (INF-α) and interleukin-2 (IL-2) are known to cause depression in cancer treatment. Such drug-induced depression is a major type of adverse drug reaction during cytokine treatment. In this article the authors show that during INF-α and IL-2 treatment there is significant decrease in tryptophan concentrations, in association with the development and severity of depressive symptoms. It is concluded that cytokine-induced depression is due to reduced availability of tryptophan.

It is highly unlikely that the women studied by Zubenko *et al* with recurrent, early-onset, familial depression have the same disorder as the cancer patients studied by Capuron *et al*, who experience full-blown depressive episodes when treated with cytokines that lower tryptophan concentrations. A challenge to our field is the development of new classification systems that go beyond syndromic concepts and use the tools of contemporary biology including genetics and genomics to develop markers that dissect the heterogeneity of psychiatric disorders.

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