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# Introduction

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This Supplement to *Metabolism* presents a collection of papers about depression that examine the subject from a variety of perspectives. Such variety—which we think beneficial—is made inevitable by the fact that the contributors represent a wide array of scientific and medical disciplines, ranging from genetics to neurosurgery. It will be noted that, despite the diversity of approaches to the subject, certain themes recur, such as the increasing evidence in support for the role of genetic makeup in rendering certain individuals vulnerable to environmental factors (notably severe stress) that may precipitate a depressive disorder.

As is evident from an examination of the papers that follow, progress in science and medicine is rarely linear—it often arises from unexpected sources (eg, a new animal model or an astute clinical observation). We are grateful that sponsorship by the Collège International de Recherche Servier has made possible the publication of a range of articles about advances in our knowledge of depression that, otherwise, would not have been available under one cover. In this way, we hope to have provided the reader with new information of clinical and research value about this devastating group of illnesses.

In his "Overview of the field," Costa e Silva, a psychiatrist, reviews the history, epidemiology, pathophysiology, and pharmacotherapy of depression. He suggests that the drug industry's current use of such sophisticated methods as genetics, high-throughput screening, and receptor imaging for development of new products needs to be given more direction. He recommends that such technology can be made more productive by employing a disease-oriented approach to guide the development of well-designed and carefully targeted, clinically efficacious drugs. He also stresses the importance of addressing psychiatric and neurological diseases at the cellular and systemic levels.

Hamet and Tremblay, in their article entitled "Genetics and genomics of depression," discuss the high prevalence and socioeconomic impact of depression and the role of gene-environment interaction in the pathophysiology of depression. Studies on the serotonin transporter (5-HTT) gene, where several copies of its short allele culminate in depression and suicide in response to lifelong stressful events, are evaluated. Studies in animal models that have contributed to the chromosomal mapping of many behavioral traits, including anxiety, the stress response, and depression, are described. Classical approaches vs use of novel models of recombinant inbred strain and recombinant congenic strain animals that allow for a rapid initial localization of any sought-for traits are discussed from the point of view of uncovering significant loci for the stress response and anxiety in rats and mice.

In "Genes, stress and depression," Wurtman points out that no aberrant genes have been shown to cause major depressive disorder in the same sense that a single defective gene causes people harboring that gene to develop Huntington's disease, regardless of how serene their environment may be. However, genes clearly can be a risk factor for developing depression, increasing the likelihood that severe environmental stresses will precipitate the onset of this illness. A relationship between genetic makeup and susceptibility to major depressive disorder (MDD) has long been suspected, based on the existence of families devastated by multiple suicides. Wurtman evaluates studies performed during the past decade on twins and then focuses on more recent investigations of gene products involved in the synthesis and actions of serotonin; among them, the serotonin uptake protein. The gene responsible for this protein exists in several alleles, and variations in the proportions of these alleles affect the ability of stressful life events to precipitate depression in

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certain young adults. Mutations in the gene that control serotonin synthesis in the human brain (tryptophan hydroxylase) also predispose to mood disturbances.

In his article entitled "Glucocorticoids, depression and mood disorders: structural remodeling of the brain," McEwen presents a comprehensive review of the mechanisms that distinguish between protection and damage of brain cells from stress. He discusses the hippocampal formation that expresses high levels of adrenal steroid receptors and is a malleable brain structure important for certain types of learning and memory and vulnerable to the effects of stress and trauma. The roles of the amygdale, an important target of stress which mediates physiological and behavioral responses associated with fear and strong emotions, and the prefrontal cortex, which plays an important role in working memory and executive function, are also discussed. McEwen considers these 3 brain regions, which are also targets for stress hormones, in the context of long-term depressive illness. He also evaluates animal models of acute and chronic stress and distinguishes between protection and damage of brain cells from stress.

In "Neurobiological basis of depression: an update," Kalia summarizes recent advances in our knowledge about the neurobiology of depression. Significant breakthroughs that have been made in genomics, imaging, and the identification of key neural systems involved in cognition, emotion, and behavior are reviewed. Novel targets that have been identified for the development of new pharmacological and behavioral treatments, as well as genetic variations associated with most mental disorders, are evaluated. New neurobiological concepts are considered as they relate to advances in mental health research such as identification of the serotonin transporter receptor, a genetic variant of which doubles the risk of depression. Brain neurochemicals, including neurotropic factors (implicated in several mental disorders), and anatomical studies involving imaging of the amygdala, hippocampus, and prefrontal cortex are highlighted. Several brain neurotransmitter systems (glutamate, $\gamma$-aminobutyric acid, serotonin, norepinephrine, and dopamine) that have been implicated in depression and mania, as well as membrane-bound signal transduction systems and intracellular signaling systems that modulate gene transcription and protein synthesis, are examined in the context of the etiology of depression. Mention is also made of the neuroimaging studies in depressed patients which have disclosed several abnormalities of regional cerebral blood flow and glucose metabolism—a surrogate of neuronal function—in various brain regions, including the limbic cortex, the prefrontal cortex, the hippocampus, the amygdala, and the anterior cingulate cortex.

In "Depression and neurosurgery: past, present and future," Nicolaidis reviews the history of surgical treatment of depression beginning in 1935, when open surgery was first used to isolate relatively large areas of the limbic system from the rest of the brain. Such "lobotomies" were followed by "selective leucotomies" and, later, by electroconvulsive therapy. Ethical questions that were raised about "psychosurgical" treatments are described and the value of using stereotaxic techniques to pinpoint surgical targets are discussed. Nicolaidis calls attention to the fact that, although neurosurgery now uses an advanced neurobiology-based, selected-lesion approach, exciting opportunities for intervening in a nondestructive fashion in certain patients with psychoses or some forms of organic brain disease have been opened up by the introduction of frequency-dependent chronic electrical stimulation. Nicolaidis examines in detail the future of frequency-dependent chronic electrical stimulation, complemented by newer techniques such as microdialysis and reverse dialysis, with concomitant functional magnetic resonance imaging and/or positron emission tomography scanning, use of chemodes for microinfusion or in situ insertion of reactivated stem cells.

In "Depression, cytokines and glial function," Miller and O'Callaghan discuss the role of cytokines made and released during systemic illness, and which can result in a constellation of symptoms strikingly similar to those observed in depression. Because of the overlap between the symptoms of depression and systemic illness, the authors suggest that cytokines may be involved in the development and maintenance of mood disorders. Cytokines are small, ubiquitous, pleiotropic molecules that are made and released in response to a variety of (often noxious) stimuli. They have a multitude of actions throughout the body, including actions in the central and peripheral nervous systems. From the evolutionary perspective, cytokines probably evolved as part of the protective mechanism that forces people to remain relatively immobile after injury or during illness. In this way, the body can use its energies and resources to fight invading microbes, or for wound repair and restoration of depleted body tissues. Alterations in the levels of circulating cytokines, especially the key proinflammatory cytokines, IL-6 and TNF-$\alpha$, have been linked to a variety of disease states, including depressive illness.

In "Subsyndromal depression in the elderly: underdiagnosed and undertreated," VanItallie points out that major depressive illness occurs in about 5.7% of US residents aged 65 years or older: however, clinically significant nonmajor (subsyndromal depression [SD]) affects about 15% of the ambulatory elderly and increases in prevalence with advancing age. He discusses the diagnosis of depression in the elderly, suggesting identification of depression (a condition often hidden in the aged) can be greatly assisted by use of age-specific screening instruments such as the Geriatric Depression Scale. In the future, brain imaging, and biochemical and physiological measurements may prove useful in confirming the diagnosis. He states that screening for late-life depression is urgently needed; first, because the condition is seriously underdiagnosed and eminently treatable; second, because, in the elderly (partic-

ularly men) with unrecognized depression, the risk of suicide is especially high.

In "Depression and cardiovascular disease: a reciprocal relationship," Plante challenges the traditional view that depression is a purely "mental" disorder and therefore in the natural domain of psychologists and psychiatrists. He cites recent epidemiological studies which have revealed that aging, physical and psychological stress, chronic pain, several metabolic disorders such as insulin resistance and established diabetes, alcoholism, inflammatory conditions, and vascular disorders such as arterial hypertension all may be associated with depression. In his review, Plante examines certain depression-associated factors and the mechanisms by which they might give rise to vascular disorders such as atherosclerosis, microcirculation endothelial dysfunction, and interstitial disturbances leading to organ damage. A number of disorders involving the circulation can lead progressively and insidiously to large artery rigidity, remodeling of peripheral arteries, and alterations of the microcirculation of large blood vessels. Perturbations in vasa vasorum blood flow may contribute to atherogenesis, in addition to the influence of numerous cellular events involved in inflammation (TNF-$\alpha$, interleukin-1-$\beta$, etc). He recommends the appropriate use of ambulatory monitoring of vascular parameters, such as heart rate and pulse pressure, and, eventually, early identification of genetic and metabolic markers, which may prove helpful in the early detection of events preceding and predicting the clinical manifestations of depression.

In "Depression in women," Noble points out that depression is the leading cause of disease-related disability in women. Epidemiological studies have shown that the lifetime prevalence of a major depressive disorder in women (21.3%) is almost twice that in men (12.7%). This ratio has been documented in different countries and ethnic groups. Noble points out that women have the greatest risk for developing depressive disorders during their childbearing years. Several biological processes are thought to be involved in the predisposition of women to depression, including genetically determined vulnerability, hormonal fluctuations related to various aspects of reproductive function, and an undue sensitivity to such hormonal fluctuations in brain systems that mediate depressive states. Psychosocial events such as role stress, victimization, sex-specific socialization, internalization coping style, and disadvantaged social status have all been considered to be contributors to the increased vulnerability of women to depression.

Finally, Claude Lenfant, in his concluding commentary, "Medical and psychiatric illness: different but concurrent," explores the interaction between mental and physical illness. He points out an often ignored fact—that depression is a frequent concomitant of somatic disorders, especially chronic illnesses and that this relationship may be bidirectional, for example, in coronary heart disease and depression, between obesity and depression, and chronic obstructive pulmonary disease and depression. Lenfant reminds us that the impact of these diseases on mortality is considerable at both individual and societal levels, especially in terms of disability-adjusted life years lost. He expresses the view that research, ranging from fundamental pursuits capitalizing on available approaches of genomics and proteomics to clinical investigations that include clinical trials testing therapeutic options, needs to be increased. He encourages experts in mental disorders and those in somatic illness to work more closely at the research and practice level so that the chronic disease patients suffering from depression will receive the full benefit of what is known.