Chapter 6

Mechanisms and Interconnections within the Functional Medicine Matrix Model

As documented in preceding chapters, there is an urgent need for an approach to treating depression that goes beyond that of conventional pharmaceutical, psychological, and other types of interventions. The prevailing conventional paradigm focuses exclusively on dysregulation in neurophysiology and psychosocial function. While clearly important, there are many other influences on depression that are usually not assessed or are given only passing notice in the conventional model. In this chapter, we will examine the scientific research on dysregulation in a variety of areas. In functional medicine, we view these diverse influences through a prism called the Functional Medicine Matrix Model (see Figure 6.1). Evaluating these core systems helps to uncover a rich collection of underlying antecedents, triggers, and mediators that may be linked to depression. Remediating underlying dysfunction is likely to have a highly beneficial effect on many patients with depressive disorders, resulting in improved outcomes for a greater number of people.

Hormone and Neurotransmitter Regulation

Hormonal imbalances are particularly relevant to the discussion of depression. There is a wealth of information implicating the stress response and hypothalamic-pituitary-adrenal (HPA) axis imbalances as triggers and mediators of depression. The research literature shows connections between depression and cortisol, thyroid, melatonin, insulin, estradiol, testosterone, and various brain neurotransmitters.

The Stress Response System and Depression

The stress response system (SRS) is the major neurophysiological basis of the mind-body connection. Stress responses and depression share many common signs, symptoms, mediators, and neural pathways. They are not synonymous, nor can depression be conceptualized solely as a dysregulation of the SRS. Nevertheless, understanding the dysregulation that occurs within the SRS is critical to an appreciation of the varying manifestations of depression and to integrating the expanded paradigm advanced in this monograph.

Depressogenic factors may originate within the body (e.g., Addison’s disease, a pituitary microadenoma), the psyche (e.g., faulty cognitions or attributions), and the environment (e.g., a failing marriage, exposure to abuse, loss of a parent, unemployment). Genetic predispositions from first-degree relatives also play a role. However, regardless of the point or points of origin, depressogenic factors are transduced bidirectionally via the SRS into morphological and functional changes within both the brain and peripheral target tissues (e.g., cardiovascular, gonadal, immune, musculoskeletal).
The SRS can be divided into both a core and a secondary aspect. The core parts of the SRS include the HPA axis and the locus ceruleus (LC). The LC is a nucleus of cells that contains virtually all of the norepinephrine-containing neurons in the brain. A single LC neuron can terminate on over 100,000 other neurons, so one can imagine the far-ranging effects of this small mid-pons nucleus. Under normal conditions, the LC helps maintain alertness. The secondary SRS includes the prefrontal cortex (PFC), the amygdala, and the hippocampus.¹

Primary mediators of the stress response include neuropeptides (corticotropin-releasing hormone [CRH], arginine vasopressin [AVP], adrenocorticotrophic hormone [ACTH]), neurotransmitters (norepinephrine, epinephrine, serotonin, glutamate, acetylcholine), and the well-known stress hormone cortisol.

Primary triggers of the stress response may be physiological (inflammation, extremes of temperature, pain, hypoglycemia, hypovolemia, excess exercise) and act directly via activation of the LC, or they may be perceptual/experiential (unbidden novelty, unpredictability, trauma, loss of control over self and self-concept) and act via the secondary SRS.

*The Acute Stress Response*

Under acute conditions of actual or perceived stress, the SRS promotes rapid, instinctual, stereotypical behaviors that generally fall into the fight-or-flight category. In potentially stressful situations, the amygdala receives sensory
input, assigns an experientially based valence (safe, arousing, or dangerous) to situations, and only then sends information to the PFC. Because of this, we often experience instantaneous gut reactions to people and events for reasons we cannot consciously explain.

Once activated, the acute stress response is manifested by both a peripheral mobilization (sympathetic activation of the autonomic nervous system) and a central change in brain function favoring an inhibition of PFC higher-order thinking and an activation of limbic and brain stem structures. This is experienced as anxiety, panic, activation, or even terrifying paralysis, all accompanied by an inability to think in an objective, thoughtful, and analytical manner (impaired executive functions of judgment, organization, planning, working memory). The stress response affects critical vegetative functions—alertness, appetite, metabolic activity, and autonomic, reproductive, neuroendocrine, immune, gastrointestinal, and psychomotor functions are all disrupted in a reverberating, bidirectional manner within the depressive experience. This linkage is one of the facts supporting a functional medicine approach to depressive disorders.

Neurophysiologically, the acute stress response is activated when the amygdala, drawing on conditioned memory stored in other parts of the brain, including the hippocampus and striatum, receives sensory input that associates an experience with danger (based on past experience). Projections from the amygdala to the norepinephrine-containing neurons of the LC are activated. The LC then transmits a norepinephrine “alarm” via its projections throughout the brain and periphery. LC projections include those to:

- The dorsolateral PFC (inhibiting its executive, higher-order thinking function)
- The lower brain stem (including serotonergic raphe nuclei and the solitary nucleus associated with anxiety)
- The autonomic nervous system (which activates the sympathetic and inhibits the parasympathetic physiology)
- The hypothalamus (which then releases CRH, AVP, and downstream ACTH and cortisol)
- The amygdala itself

The amygdala, activated by this positive feedback loop mediated by norepinephrine, CRH, AVP, and cortisol, releases its own stores of CRH to continue the feedback loop. Once the stressor has been removed, the system re-establishes homeostasis; however, key elements of the situation have been stored (by the amygdala, hippocampus, and striatum) for future reference.²
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The Chronic Stress Response in Depression

The physiological wear and tear that the body experiences due to repeated cycles of stress, during which it attempts to maintain stability via continuous rebalancing, has been termed allostasis (maintaining stability or homeostasis through change). Allostatic load is the cumulative physiological strain that is required to maintain homeostasis. Markers of allostatic load are being refined and tested. At the current time, they are thought to include 10 variables, six of which seem to be related to metabolic syndrome (HgA1c, waist-hip ratio, HDL, total cholesterol, systolic and diastolic blood pressure) and four of which are related to the HPA axis (urinary epinephrine, norepinephrine, cortisol, DHEA-S).

Cumulative measures of allostatic load are a significant predictor of all-cause mortality, cognitive decline, physical functioning, and cardiovascular disease for as long as 7.5 years after initial measurement. (For an overview of the effects of acute and chronic stress, both psychological and physical, see Tatum in the Textbook of Functional Medicine.)

Depression exhibits characteristics of a chronically activated SRS, resulting in an increased allostatic load. The mediators and consequences of chronic stress have all been associated, in one way or another, with depression. As described above, the primary mediators of the stress response include CRH, AVP, ACTH, cortisol, DHEA, DHEA-S, norepinephrine, and epinephrine. Secondary pathways include cellular responses such as second and third messenger activation, enzymatic activation, receptor modulation, short- and long-term potentiation, apoptosis, and changes in neurotrophic factors, glial cell function, and immune parameters including cytokines. At a tertiary level, these processes are evident in altered markers that reflect a summation and integration of the secondary processes, such as blood pressure, heart rate, and HgA1C. At the quaternary level are diagnosable diseases (e.g., heart diseases, diabetes, cognitive impairment).

The onset of depression may be due to many factors, including:

- The persistence of a chronic and real stressor (e.g., a state of externally induced helplessness over one's career or finances due to illness; war; in a child, an abusive or abandoning parent)
- The triggering of a biological or genetic program (e.g., a severe inflammatory disorder or a strongly heritable disorder)
- A failure to realign one's beliefs or actions as part of an adaptive response to a life situation (e.g., giving up an idealized view of marriage)
- A skill deficit (e.g., a child with an unrecognized learning disability who is trying to achieve normally)

Regardless of cause, however, the SRS seems to become and remain dysregulated as part of the genesis and maintenance of the depressive condition. In the midst of this chronic activation, the depression is transduced into physical manifestations that are the basis for the comorbidity associated with depression.

Clinical Pearl:

I recently noted the lingering effects of the acute stress response in a patient who had depression accompanied by an attachment problem. Her mother’s affect was always extreme and unpredictable, invoking repeated fear/danger responses in the patient. When the patient came in for a visit after an extended absence, she was highly anxious because she didn’t know how I was going to behave. This anxiety made it quite difficult for her to direct the conversation in any meaningful way. She calmed down immediately when I identified the fear and gave her information about what I was doing. Within seconds of knowing that she was not in danger from me, she began to direct the conversation to her real concerns.
Cortisol and Adrenal Fatigue

The HPA axis has major interactions with the hypothalamic-pituitary-gonadal (HPG) and reproductive hormone axes, the thyroid axis, the growth hormone axis, glucoregulation, insulin resistance, and Th1/Th2 balance. Abnormalities of all these perpetuate the cycle of depression.\(^8\) For example, a person who is repeatedly hypoglycemic (perhaps due to poor diet, chromium deficiency, or high levels of stress and pain) will, over time, stress the adrenal axis. The stress response is quite complex and the levels of cortisol, DHEA, other adrenal steroids, and catecholamines vary with the duration of the stress, genetic factors, and the consequent phase of adrenal insufficiency or overstimulation. Depending on the duration of the stresses, genetic factors, early life experiences, and factors affecting resilience (e.g., social support), the pattern and severity of adrenal axis dysfunction, as seen on the salivary adrenal index and measures of catecholamine turnover (e.g., 24-hour urinary catecholamines), will differ.\(^9\) Early in the stress response (in this example, it is secondary to hypoglycemia), one might see elevated cortisol and catecholamines, but with time (months or years of repeated and frequent hypoglycemic episodes), poor nutrition, and continued stressors, the system’s ability to produce cortisol, DHEA, and other adrenal steroids may be reduced and reserves of catecholamines depleted, leaving the patient fatigued, exhausted, and unable to mount an adequate stress response on an hour-to-hour and situation to situation basis. This can easily present to the clinician as depression. Some studies, but not all, support the efficacy of DHEA use in depression, often with supraphysiological doses.\(^{10,11}\)

Thyroid Dysfunction

The thyroid axis is closely aligned with central beta-receptor function, DNA expression of neurotrophic factors, serotonergic and noradrenergic receptor function,\(^{12}\) and melatonin. This alignment is thought to underlie the finding that although the vast majority of patients with major depression are euthyroid, the condition often coexists with autoimmune subclinical thyroiditis, suggesting that depression may alter the immune system or that it may be an autoimmune disorder itself.\(^{13}\) According to a 2006 review article, “It is clear that depression is not characterized by an overt thyroid dysfunction, but it is also clear that a subgroup of depressed patients may manifest subtle thyroid abnormalities, or an activation of an autoimmune process.”\(^{13}\) Evidence of causality is conflicting, since changes in the hypothalamic-pituitary-thyroid (HPT) axis could be either causes or consequences of affective disorders; in addition, the cause could be thyroid peroxidase antibodies and not thyroid hormone levels, per se.

Recent evidence of thyroid dysfunction in depression includes the following:

- A prospective cohort study found that patients hospitalized with hypothyroidism had a greater risk of readmission with depression or bipolar disorder than control patients hospitalized with either osteoarthritis or nontoxic goiter.\(^{14}\)
- 23% of 60 depressed patients with “high-normal” (3.00–5.50 mIU/L) TSH levels had an exaggerated TSH response on the thyrotropin-releasing hormone stimulation test. This prevalence was significantly greater than the 6% prevalence of positive stimulation test results reported in the euthyroid general population.\(^{15}\)
- In a population of chronically depressed patients referred to a mood disorders unit, 22% of those referred with treatment-resistant depression had evidence of clinical or subclinical hypothyroidism compared with 2% of those with non-treatment-resistant depression.\(^{16}\)
- Mean antenatal T4 concentrations and free T4 indices correlated significantly and negatively with mean depression scores during each of 3 postpartum time periods.\(^{17}\)
- Subjects with at least one diagnosis of anxiety or mood disorders were positive for serum antithyroid peroxidase more frequently than subjects without mood or anxiety disorders.\(^{18}\)

T3 therapy has been shown to improve patient response when used to augment antidepressants in treatment-resistant depression.\(^{19,20}\) (See Strategies for Enhancing Antidepressant Effectiveness in Chapter 4.) A 2006 review\(^{12}\) described a possible mechanism: administration of a combination of fluoxetine and T3 induced reductions in the
transcription of the 5-HT1A and 5-HT1B autoreceptors, which mediate serotonergic neurotransmission by feedback actions at the levels of cell firing and neurotransmitter release. It has been suggested that T3 may be beneficial in approximately 25% of depressed patients.\textsuperscript{21}

There is also evidence showing the effectiveness of T4 as an antidepressant augmentation strategy.\textsuperscript{22} A 2000 review of 8 open clinical trials reported: “Augmentation with supraphysiological doses of T4 has antidepressant and prophylactic effects in roughly 50% of patients completely resistant to all other antidepressant and prophylactic therapies.... It has also consistently been shown that high serum concentrations of T4 predict favorable response to antidepressant treatment and that the serum levels of T4 decrease in responders to these treatments, but not in non-responders.”\textsuperscript{23}

**Circadian Rhythm and Melatonin**

Evidence for a dysfunction in circadian time keeping in depression includes the cyclic nature of depressive illness, the diurnal variations in its symptomatology, and the existence of disturbed sleep-wake and core body temperature rhythms. Thus, the rhythm regulator melatonin has received attention as a marker of mood disorders. “Measurement of melatonin either in saliva or plasma, or of its main metabolite 6-sulfatoxymelatonin in urine, have documented significant alterations in melatonin secretion in depressive patients during the acute phase of illness. Both the levels and the timing of melatonin secretion are altered in bipolar affective disorder and in patients with seasonal affective disorder (SAD).”\textsuperscript{24} While melatonin treatment has been shown effective in treating circadian rhythm disorders as well as insomnia, the inference that it would also influence affective disorders has not been completely borne out.\textsuperscript{25} However, bright light treatment that suppresses melatonin production is effective in treating bipolar affective disorder and SAD, winter type,\textsuperscript{24} and this intervention also showed some clinical response in non-seasonal depression in a randomized controlled trial (RCT).\textsuperscript{26}

New avenues for treatment in this area have focused on compounds with activity at melatonergic receptors. In several clinical trials, agomelatine, a compound with agonistic properties at MT1 and MT2 receptors and antagonistic properties at the 5-HT2C receptor, has been found superior to placebo, with suggested superior efficacy to currently available antidepressants. The rate of effect and overall tolerability profile of agomelatine also suggests a clinical advantage over selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs).\textsuperscript{27} For a larger discussion, see a review\textsuperscript{25} of the antidepressant mechanisms of agomelatine, as well as studies of melatonin in depression.

**Reproductive Hormones**

Estradiol, testosterone, and other reproductive hormones interact with brain neurotransmitters.\textsuperscript{28-30} In particular, altered levels of estrogens can have mood-altering effects for many different reasons. These alterations are thought to occur via direct estrogen effects on cell surface receptors or gene expression (e.g., altered genetic dendritic formation in the hippocampus during different phases of the menstrual cycle)\textsuperscript{31} or via increased or decreased availability of catecholamines due to competition for catechol-O-methyltransferase (COMT); this competition for COMT is especially significant in individuals with reduced COMT enzymatic activity due to single nucleotide polymorphisms (SNPs) or undermethylation.\textsuperscript{32} Recent research has indicated that estradiol impacts CRH gene expression.\textsuperscript{33} This suggests a link between estrogen and the HPA axis, which is so central to the biological aspects of depression.

The intricate association between the HPG and HPA axes (the HPA axis directly inhibits gonadotropin-releasing hormone) is exemplified by increasing rates of depression in women of reproductive age; by increased risk of depression for women who are perimenopausal or postmenopausal or in the postpartum stage; and by the responsiveness of perimenopausal and menopausal depression,\textsuperscript{34-36} premenstrual depression,\textsuperscript{37} and postnatal depression\textsuperscript{38} to
transdermal estrogen. For postmenopausal women, however, hormone replacement therapy (estrogen plus proges-
terone or estrogen alone) was no more effective than placebo in some studies.

Approximately 20% of men in their 60s and 50% of men over the age of 80 demonstrate low testosterone levels. This age-associated hypogonadism is associated with some symptoms that overlap with depression, but the exact association is unclear. Two recent studies have found that low testosterone levels predicted earlier onset and greater incidence of depressive illness, but studies of testosterone replacement in depressed men were conflicting. Similarly, it has been proposed that replacement of DHEA may improve mood and libido in both men and women. Although there is some limited evidence of mood-enhancing effects of DHEA, particularly in populations with adrenal insufficiency, the literature does not currently support its therapeutic use in this area, and more defined and specific clinical trials are needed. In addition, risks of long-term supplementation with either testosterone or DHEA are unknown.

**Glucoregulation**

The association between affective disorders and alterations in glucose utilization is well established. (See Chapter 3 for a discussion of diabetes and depression.) Depressed patients demonstrate significantly higher basal glucose levels, greater cumulative glucose responses after an oral glucose tolerance test, and larger cumulative insulin responses after an oral glucose tolerance test than control subjects, indicating a functional state of insulin resistance during major depressive illness. While several studies found that the severity of depressive symptoms increased the risk for insulin resistance, other research was contradictory. In a 2006 study, insulin sensitivity increased in nondiabetic patients after successful treatment with an SSRI or a tricyclic antidepressant (TCA). A possible explanation for insulin resistance in depressive disorders (and Alzheimer’s disease) holds that inadequate glucose utilization underlies neuronal changes in crucial brain regions (i.e., the limbic system), and in patients with undetected or untreated insulin resistance, such changes in glucose utilization may lead to neurodegeneration. A 2002 review postulated that insulin resistance may be the link between depression and atherosclerotic vascular diseases.

**Immune Surveillance**

Immune system dysfunction and dysregulation—with or without an inflammatory association—have significant relationships with depression. Supporting the concepts advanced in this monograph, there is recent and mounting evidence that both glial cells (as active participants in synaptic transmission, supporters of neuronal function, clearance agents for neurotransmitters such as glutamate from the synapse, and modulators of synaptic plasticity) and glutamate are involved in depressive disorders and that the immune system is disturbed both peripherally and centrally in depression. At least one recent study reported a response to riluzole augmentation for patients with treatment-resistant depression; riluzole targets glutamate neurotransmission.

Additionally, lamotrigine, a glutamate inhibitor, has recently been documented to have antidepressant effects in unipolar depression in 2 small studies. While the specific pathways by which glutamate and glia influence mood disorders are not fully understood, current thought indicates that activation of the proinflammatory cytokines activates the tryptophan- and serotonin-degrading enzyme system indoleamine 2,3-dioxygenase (IDO), which may contribute to the serotonergic dysregulation in depression. IDO and its subsequent enzyme kynurenine monooxygenase increase production of quinolinic acid, a strong agonist of the ionotropic (fast-acting) glutamatergic N-methyl-D-aspartate (NMDA) receptor. Glutamatergic overactivity is generally thought to be neurotoxic via calcium-mediated apoptotic pathways. In addition, the metabotropic glutamatergic receptors (involved in the long-term modulation of glutamate transmission) can facilitate the release of serotonin, norepinephrine, and dopamine. This imbalance in glutamate activity is normally counteracted by a subset of glia, the astrocytes, whose numbers are reduced in depression. Thus, imbalances in the immune-neurotransmitter systems are likely to form part of the genesis or maintenance of some forms of depression.
Another line of evidence supporting the role of the immune system in mood disorders stems from the fact that several illnesses characterized by disturbances in the immune system (e.g., lupus, rheumatoid arthritis, celiac disease) are often accompanied by depression, as discussed in Chapter 3. While hypotheses regarding the connection between psychiatric symptoms and autoimmune abnormalities have yet to be proved, there is strong evidence that the same alterations in immunity may play a role in the pathophysiology of both depressive symptoms and these inflammatory disorders. A 2006 review summarizing the evidence for a cytokine-mediated pathogenesis of depression and fatigue in multiple sclerosis reported that peripheral and central production of cytokines may account for some of the behavioral symptoms that cannot be explained by psychosocial factors or central nervous system (CNS) damage. In fact, emerging clinical data from multiple sclerosis patients support an association of central inflammation, as measured by MRI, and inflammatory markers with depressive symptoms and fatigue.

Does delayed food sensitivity (i.e., IgG food allergy) result in an IgG immune complex-induced activation of inflammation? Could this contribute to depression? When one begins to appreciate the link between the immune system, the HPA axis, and the endocrine system, the possibility that food and mood are linked via an immune response to food (the intestines contain nearly 70% of the body’s immune cells) becomes plausible. Recent research using the 2002 Canadian Community Health Study confirmed an association between allergies and mood and anxiety disorders in a general population sample.

**Inflammatory Process**

Immunologically, central CRH inhibits inflammation via glucocorticoids and catecholamines, but immune CRH stimulates inflammation. Numerous inflammatory abnormalities have been associated with depression, including changes in acute-phase proteins and cytokines. These products of immune activation are known to have direct effects on the HPA axis, the sympathetic nervous system, energy balance, and neuronal function.

The cytokine hypothesis of depression suggests that the nervous system, the endocrine system, and the immune system are reciprocally linked as both triggering and mediating pathways of depression. In this view, a variety of proinflammatory cytokines (IL-1, IL-6, TNF-alpha, gamma interferon) act as neuromodulating mediators affecting behavioral, neurochemical, and endocrine features of depressive disorders. The cytokines are thought to account for the HPA overactivity characteristic of melancholic depression, since cytokines are known to cross and influence the blood-brain barrier (if produced peripherally) and to disturb the negative feedback inhibition of corticosteroids in the HPA axis. Major bodies of evidence supporting this aspect of depression include:

- A significantly increased risk for suicide has been associated with asthma and seasonal allergy.
- In a recent national epidemiological study in the United States, a doubling of the rate of suicide in women during periods of highest pollen counts was demonstrated, after adjustment for environmental light.
- In a double-blind, crossover study involving 20 healthy males without a history of psychiatric disorder, subthreshold doses of non-infectious endotoxin induced elevation of specific cytokines, including TNF-alpha and IL-6, associated with significantly increased anxiety, impaired memory, and depressed mood.

According to Dantzer, it is possible to describe a very close connection between inflammation, illness, and depression:

“In response to a peripheral infection, innate immune cells produce pro-inflammatory cytokines that act on the brain to cause sickness behavior. When activation of the peripheral immune system continues unabated, such as during systemic infections, cancer or autoimmune diseases, the ensuing immune signalling to the brain can lead to an exacerbation of sickness and the development of symptoms of depression in vulnerable individuals. These phenomena might account for the increased prevalence of clinical depression in physically ill people. Inflammation is therefore an important biological event that might increase the risk of major depressive episodes, much like the more traditional psychosocial factors.”
Interestingly, in a 2005 study, IL-6 levels were significantly lower after treatment with SSRIs in both patients with major depressive disorder and healthy controls. In a 2007 study, depressed patients who did not respond to SSRIs had significantly higher levels of IL-6 and TNF-alpha than both euthymic patients who were formerly SSRI resistant and healthy controls.

Subtle inflammatory signals that have been shown to be factors in cardiac pathology have also been associated with depression. Several studies have shown that acute-phase proteins including high-sensitivity C-reactive protein and amyloid-A increase in depression. The acute-phase response begins with the release of proinflammatory cytokines IL-1 and TNF, which stimulate the release of copious amounts of IL-6 by peripheral cells, including vascular smooth muscle. In response to IL-6, the liver shifts from the synthesis of “housekeeping” proteins such as albumin toward production of acute-phase reactants, which are thought to play a key role in cardiovascular diseases.

The rise in markers of stress and inflammation that occurs in depression also underscores the link between affective illness and metabolic syndrome. A 2007 study was the first to demonstrate that depressive symptoms, stressful life events, and frequent feelings of intense anger and tension predicted the risk for developing metabolic syndrome, as defined by multiple definitions. The authors noted that psychosocial factors are associated with alterations in the autonomic nervous system (e.g., elevated heart rate and reduced heart rate variability), the HPA system (e.g., elevated cortisol), and hemostatic and inflammatory markers (e.g., heightened platelet aggregation, fibrinogen, proinflammatory cytokines, white blood cell count). “All of these physiological changes have been recognized as important in the development of the metabolic syndrome.”

Another emerging pathway between depression and inflammation involves melanocyte-stimulating hormone (MSH). According to Lipton, “Alpha-MSH modulates all forms of inflammation by acting on peripheral inflammatory cells, [central] glial inflammatory cells, and on CNS receptors that activate descending anti-inflammatory neural pathways.” MSH interacts with the nearby melatonin receptor to regulate restorative, restful sleep. MSH is made by cleavage of a parent molecule, proopiomelanocortin (POMC), following activation of the long isoform of the leptin receptor, a cytokine receptor. Production of MSH is accompanied by production of beta-endorphin. Deficiency of MSH will result in absence of restorative restful sleep and abnormal perception of pain due to melatonin and endorphin problems, respectively. Many people with MSH deficiency will have cytokine-driven leptin resistance; the adipose tissue-derived hormone leptin acts via its receptor (LRb) in the brain to regulate energy balance and neuroendocrine function (e.g., MSH).

This information supports the use of anti-inflammatory strategies in the treatment of depression, including (as appropriate to the patient) reduction of proinflammatory triggers and their mediators (e.g., identifying food sensitivities and withdrawing offending foods, reducing exposure to respiratory allergens and toxins); treatment of chronic infections; normalization of insulin and glucose regulation; and use of anti-inflammatory compounds such as curcumin (turmeric) or COX-2 inhibitors. Several recent studies on the effects of curcumin in chronically stressed rats have confirmed its antidepressant activity, related to its modulating effects on the HPA axis, hippocampal neurons, and serotonergic receptors. Similarly, stressed mice treated with the COX-2 inhibitor celecoxib had lower levels of proinflammatory cytokines than stressed mice who did not receive the treatment, and another experiment suggests additional neuroprotective and antioxidant functions of these medications under stress-induced conditions.

**Digestion, Absorption, and Barrier Integrity**

The alimentary tract and its accessory organs (liver, gallbladder, and pancreas), the gut-associated lymphoid tissue (GALT), the active microbial populations, and the epithelial barrier that separates the outside environment from the inside all constitute important areas for consideration when looking at patients with depression. Numerous studies using animal models have shown that stress can trigger colonic epithelial barrier dysfunction via effects on mast cells, gamma interferon, and myosin light chain phosphorylation. This decrease in gut barrier function in turn leads to excessive uptake of luminal material. Thus, depression can increase vulnerability to intestinal...
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Inflammation. Research has shown that the presence of an oral antigen during chronic psychological stress altered the immune response to sensitization and caused subsequent antigen-induced gut pathophysiology in rats. In a separate study on mice, pups separated from their mothers had a more severe colitis than those who were not separated. In addition, antidepressant therapy improved parameters of depressive-like behavior and reduced vulnerability to dextran sulphate colitis. Chronic stress has also been shown to increase bacterial uptake in follicle-associated epithelium. Interestingly, in a study that exposed rats to water-avoidance stress, researchers found that pretreatment with probiotics completely prevented stress-induced bacterial adhesion and translocation of bacteria to mesenteric lymph nodes.

Conversely, it has been hypothesized that digestive imbalances can contribute to affective disorders by causing limited nutrient absorption. For example, aging patients, those with Helicobacter-induced chronic gastritis, and those who take H2 receptor antagonists often have low-functioning parietal cells in the stomach, resulting in reduced production of hyperchloric acid (stomach acid). This has multiple consequences, including increased risk of constipation and small intestinal bacterial overgrowth (SIBO). Additionally, absorption of vitamin B12 may be reduced when release of intrinsic factor is impaired. Cater reported that “small intestinal bacterial overgrowth in hypochlorhydria probably leads to putrefactive breakdown of the metabolically useful products of protein digestion, thereby reducing their availability for certain essential pathways. The possible lowering of tryptophan, tyrosine, and phenylalanine in the blood may be a precipitating factor in depression in hypochlorhydric patients.”

Indeed, there is evidence that inadequate digestion (or ingestion) of protein can result in dysthymia, resistance to antidepressant treatment, or depressive relapse. Tryptophan depletion induces marked reduction in plasma tryptophan, as well as brain serotonin synthesis and release. Depressive symptoms are common in celiac disease, and at least 2 studies suggest that the cause is impaired availability of tryptophan. In several studies, experimental lowering of serotonin neurotransmission by acute tryptophan depletion induced a transient depressed mood in 50% to 60% of remitted depressed patients treated with an SSRI. (However, in currently depressed patients, tryptophan depletion may augment response to an SSNRI.) In additional, catecholamine depletion via a tyrosine hydroxylase inhibitor reversed the therapeutic effects of norepinephrine reuptake inhibitors (NRIs) but not SSRIs.

Bidirectional communication occurs between the CNS and the enteric nervous system, occurring along what has been termed the gut-brain axis. A 2004 review characterized irritable bowel syndrome (IBS) as a model for these gut-brain interactions: “Various non-site specific neurotransmitters influence gastrointestinal, endocrine and immune function, as well as human behavior and emotional state, depending on their location. The physiology of the digestive tract, the subjective experience of symptom, health behavior, and treatment outcome are strongly affected by psychosocial factors.” Psychiatric disorders, especially major depression, anxiety, and somatoform disorders, occur among 20 to 50% of IBS syndrome patients. Our understanding of the role of neurotransmitters in IBS has been strengthened by studies showing that corticotrophin-releasing factor (CRF) plays a major part in stress-related gastrointestinal alterations, and in fact, CRF1 receptors are now being investigated as a therapeutic target for IBS.

Detoxification and Biotransformation

Toxins and their biotransformation constitute an important area in relationship to depression. As will be shown, certain toxic metals can have a subtle yet profound effect on mood. Additionally, biotransformation of drugs and endogenously produced hormones can have an important effect on brain function. Consider that the vast majority of psychotropic medications are metabolized in the liver; steroid hormones (e.g., estrogen, testosterone) known to have an effect on mood disorders are metabolized in the liver; and levels of hormones and drugs can become toxic through hepatic recirculation. Thus, the efficacy with which an individual detoxifies these substances can increase or decrease their effect.

The detoxification systems must rid the body of toxins such as xenobiotics, which can cause neurological damage. For example, lead exposure has been linked with biochemical and functional changes in the heme biosynthetic
pathway and in the renal, cardiovascular, endocrine, immune, and nervous systems. As Needleman determined 20 years ago, “Encephalopathy generally occurs at blood lead levels of 80 µg/dL or more, but unequivocal brain damage has been demonstrated at doses well below this level. At lower doses, the neurocognitive effects of lead are expressed as diminished psychometric intelligence, attention deficits, conduct problems, alterations in the electroencephalogram, school failure, and increased referral rates for special needs.”

In addition to its direct physiological effects, lead is associated with deficiencies in body calcium, zinc, iron, and protein stores. Lead also has been shown to cause increased neuropsychiatric symptoms, including mood disorders, many years after exposure. One psychiatrist has written a personal account of the effects of lead poisoning in his patients. A 2000 study showed a significant dose-response relationship between career solvent exposure, blood lead level, and personality symptoms in journeyman painters. “Results showed that the probability of being diagnosed with a mood disorder differed significantly in painters (41%) and control subjects (16%)…. Painters exhibited a sub-clinical pattern of personality dysfunction involving symptomatology that was measured allowing for late onset (after age 25)."

There is also evidence that mercury can induce depression-like behavior. A 2007 review on methylmercury reported: “Several mechanisms have been suggested from in vivo and in vitro studies, such as effects on neurotransmitter systems, induction of oxidative stress and disruption of microtubules and intracellular calcium homeostasis. Recent in vitro data show that very low levels of methylmercury can inhibit neuronal differentiation of neural stem cells.” Depresssion has recently been associated with long-term mercury exposure in former mercury miners and workers in a florescent lamp factory. Additionally, exposure to both arsenic and manganese has been linked to depression, among other conditions.

A large body of evidence has accumulated on the role of organophosphorus and carbamic pesticides on hormonal function. Epidemiological studies conclude that acute and chronic pesticide exposure is associated with affective disorders, and a causal association has been shown between pesticide use and suicide.

The harmful effects of substances produced by fungi, especially molds, are now being elucidated. Ochratoxin-A is an immunosuppressant mycotoxin produced by species of Aspergillus and Penicillium in a wide variety of climates and geographical regions. This compound damages the CNS through a complex mechanism that includes evocation of oxidative stress, bioenergetic compromise, inhibition of protein synthesis, production of DNA single-strand breaks, and formation of ochratoxin-A-DNA adducts. Researchers investigating ochratoxin A’s effects on the mouse brain recently concluded, “Overall, these results lead to speculation that ochratoxin-A exposure may contribute to impaired hippocampal neurogenesis in vivo, resulting in depression and memory deficits, conditions reported to be linked to mycotoxin exposure in humans.

Oxidative/Reductive Homeodynamics

A chief complaint of depressed patients is low energy. Ultimately, energy production occurs at the level of the mitochondria in various tissues of the body, and we know that oxidative stress can impair mitochondria functioning. In addition, oxidative stress increases inflammation and cytokine production, initiating a cascade that impacts endocrine and CNS function. A recent literature review found a solid foundation for the hypothesis that oxidative mechanisms serve as a unifying pathogenesis in psychiatric disorders, including depression.

Moretti et al reported:

“There is increasing evidence that affective disorders are associated with dysfunction of neurotransmitter postsynaptic transduction pathways and that chronic treatment with clinically active drugs results in adaptive modification of these pathways... Despite some inconsistencies, PET and SPECT studies suggest low activity in cortical (especially frontal) regions in depressed patients, both unipolar and bipolar, and normal or increased activity in the manic pole. Preliminary MRS studies indicate some alterations in brain metabolism, with reduced creatine phosphate and ATP level in the brain of patients with affective disorders."
Other studies have suggested that mitochondrial dysfunction is an important component of bipolar disorder.\textsuperscript{143} Energy transduction dysregulation may involve the enzymatic systems of the Krebs cycle, the electron transfer chain, oxidative phosphorylation, or the enzyme activities of ATP-requiring ATPases.

A recent study examined the possibility that oxidative stress might contribute to the PFC and hippocampal volume reductions that have consistently been found in patients with recurrent depressive disorder. The concentration of copper/zinc superoxide dismutase was significantly increased in postmortem PFC, but not hippocampal, tissue in depressed patients vs. controls.\textsuperscript{144} Other investigations have found significantly higher plasma malondialdehyde, adenosine deaminase, xanthine oxidase, and susceptibility of red blood cells to oxidation in depressed patients than in controls. Researchers recently reported that red blood cell superoxide dismutase activity was significantly increased in depressed patients and that there was a positive correlation between severity of the disease and superoxide dismutase activity.\textsuperscript{145}

Fluoxetine,\textsuperscript{146} escitalopram,\textsuperscript{147} venlafaxine\textsuperscript{148} and other psychiatric drugs have been shown to reverse or prevent oxidative damage in depression-induced rats. Interestingly, fluoxetine and turmeric had similar efficacy in preventing restraint stress-induced oxidative damage in one study.\textsuperscript{146} Taken together, the science indicates that reducing oxidative stress and increasing antioxidant defenses can play a role in depression treatment.

### Structural Integrity

In general, the literature indicates that people who participate in physical activity are less likely either to have depression or to develop depression in the future. A 2006 review article reported, “We confirm that there is irrefutable evidence of the effectiveness of regular physical activity in the primary and secondary prevention of several chronic diseases (e.g., cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis) and premature death.”\textsuperscript{149} Unsurprisingly, all of these chronic diseases are connected through the mechanisms described in this discussion, as well as through their comorbidity with depression, as presented in Chapter 3.

A key factor in the preventive quality of exercise is its acute and chronic anti-inflammatory effect. Although the mechanisms for this anti-inflammatory effect have not yet been fully elucidated, several compelling mechanisms presented in another review\textsuperscript{150} include loss of body fat, reductions in macrophage accumulation in adipose tissue, altered macrophage phenotype in adipose tissue, exercise-induced muscle production of IL-6, and alterations in the balance between the sympathetic and parasympathetic nervous systems.

In particular, aerobic exercise at a dose consistent with public health recommendations (17.5 kcal per kilogram per week) was found to be an effective treatment for major depressive disorder of mild to moderate severity in a comprehensive RCT.\textsuperscript{151} To give a real world example of this exercise dose, a man weighing 70 kg (154 lb) exercising to a heart rate of 145 beats per minute on a treadmill expends approximately 350 kcal in 30 minutes, requiring approximately 100 minutes of exercise per week.\textsuperscript{152} In 2 studies on one population, aerobic exercise was as effective as sertraline in treating depression and more effective at preventing relapse.\textsuperscript{152-154} Examining the effects of exercise on mental health in general, a more recent study found that relative increases in maximal cardiorespiratory fitness and habitual physical activity were cross-sectionally associated with lower depressive symptomatology and greater emotional well-being.\textsuperscript{155}

Research on exercise and depression has concentrated on aerobic training because this type of exercise is focused on elevating the heart rate and expending caloric energy.\textsuperscript{156} However, exercise prescriptions commonly include strength training in addition to aerobic exercise. A recent study found that strength training was positively associated with perceived health and modestly negatively associated with depression, anxiety, and suicidal ideation in female college students.\textsuperscript{157} The American College of Sports Medicine has also recommended strength training for older adults, noting that it can offset the loss in muscle mass and strength typically associated with normal aging, greatly improving functional capacity and quality of life in this population.\textsuperscript{158}
Psychological and Spiritual Equilibrium

We have already described the physiological mechanisms by which stress leads to neuroendocrine-immune changes. Moving further up the chain of events, psychological, psychosocial, and spiritual factors are also crucial elements. Identifying and evaluating each factor affecting a patient’s mental health is a great challenge, one that cannot be encompassed in a single monograph. As examples, however, marital stress, job stress, financial stress, personal illness, and a loved one’s death or illness can have a major impact on psychological health. It is clear that stress experienced as a child can cause lifelong disruptions in HPA axis functioning, but the literature also shows that maternal stress can affect the fetal brain, thereby influencing the mental health of children before they are born.

Numerous studies have found that neighborhood context and socioeconomic status also play a role in the quality of health, including mental health. Pathways by which these factors can affect health include:

- Involvement of the SRS as a result of cognitive appraisal of potential helplessness or harm (e.g., low job control)
- Direct effect of health behaviors (e.g., diet, exercise, smoking)
- Neighborhood effects (e.g., availability of municipal services, perceptions of neighborhood safety)
- Social support

A 2003 meta-analysis found that individuals with low socioeconomic status had higher odds of being depressed (odds ratio = 1.81, \( p < 0.001 \)), but the odds of a new episode (odds ratio = 1.24, \( p = 0.004 \)) were lower than the odds of persisting depression (odds ratio = 2.06, \( p < 0.001 \)). A dose-response relationship was observed for education and income. A 1998 study of affluent older adults also found that increasing income level was associated with lower levels of depressive symptoms. However, this association was not statistically significant when measures of health conditions, physical disability, and social support were included in the model.

While the conclusion remains controversial, associational data do suggest that patients who report greater spirituality are more likely to report fewer depressive symptoms. A 2004 survey among patients at an urban primary care clinic indicated that the quantity of one’s religious practices were less important than the quality. Quantity of prayer and attendance of religious services did not make a difference in depressive symptoms in this population, yet belief in a higher power, having a relationship with a higher power, and belief in prayer showed significant difference between depressed and nondepressed individuals. The authors acknowledged that lack of faith may merely be another symptom characterizing clinical depression, but they also suggested that among patients whose life pressures can be severe and depression levels high, “encouraging appropriate involvement in spiritual activity or incorporating religious imagery in a therapeutic regimen may have a benefit.”

For more complete reviews of psychological and spiritual effects on mental health, please see Liska and Heday in the Textbook of Functional Medicine.

Nutritional Status

B Vitamins

Many studies show an elevated incidence of folate deficiency in depressed patients; often about one third of depressed patients were deficient. In addition, therapeutic outcomes are worse and relapse rates are higher in folate-deficient patients (see Abou-Saleh and Coppen for a review).

A 2004 meta-analysis concluded that folate may have a potential role as a supplement to other treatments for depression, though it is currently unclear whether that is the case for both people with normal folate levels and those with deficiency. (See Strategies for Enhancing Antidepressant Effectiveness in Chapter 4.)
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has suggested that 2 mg of folic acid should be given during the acute, continuation, and maintenance treatment of depression. Two articles serving as evidence for this conclusion are:

- 109 patients with major depressive disorder completed a 10-week trial of either 20 mg of fluoxetine with 500 µg folic acid or fluoxetine with a placebo capsule. Ninety-four percent of the women showed a therapeutic response on the folic acid arm (>50% reduction in Hamilton Rating Scale score) as compared with 61% of the women who received fluoxetine only. Men showed no clinical response, but their plasma folate levels increased by less than half of that of the women. Abou-Saleh and Coppen suggested that the 500 µg dose may have been too low to produce a difference in men.
- In a 1990 study, 41 patients with methylfolate deficiency and acute psychiatric disorders received either 15 mg of methylfolate or placebo in addition to standard treatment. The patients receiving methylfolate showed a significant improvement after 3 and 6 months.

Low vitamin B12 status has also been found in studies of depressed patients. In a 2000 study of 700 disabled, non-demented, community-dwelling women over age 65, B12 deficiency was associated with a 2-fold increase in the risk for severe depression. B12 deficiency was present in 17% of women with mild depression (n=100) and 27% of those with severe depression (n=122). A more recent study found significantly lower levels of B12 (and folate) in 33 subjects with depression vs. 33 healthy controls in an elderly community. Homocysteine was also significantly higher in the depressed individuals.

Evidence of B12’s effectiveness in treating depression is scarce, but a 2007 double-blind, placebo-controlled study found that supplementation improving B12 (and folate) status reduced depressive symptoms in hospitalized, acutely ill older patients. In addition, another study found a significant association between B12 status and 6-month treatment outcomes for major depressive disorder.

While a complete discussion of mechanisms is beyond the scope of this monograph, the following findings are worth noting:

- A plausible explanation for the association of folic acid and depression implicates serotonin. In most of the relevant studies, low folate deficiency was associated with low levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid, and in one study, supplementation with folate restored these levels to normal. There is also a decrease in serotonin synthesis in patients with MTHFR deficiency, a disorder of folate metabolism.
- Folate and B12 are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAMe) is formed. SAMe donates methyl groups that are crucial for neurological function. Folate deficiency decreases SAMe in the rat brain. In humans, SAMe is an antidepressant and increases cerebrospinal fluid levels of 5-hydroxyindole acetic acid (5-HIAA), a marker of serotonergic function.
- Increased plasma homocysteine is a functional marker of both folate and B12 deficiency, and increased homocysteine levels are found in depressed patients. Furthermore, the MTHFR C677T polymorphism that impairs homocysteine metabolism is shown to be overrepresented among depressive patients. (See Folstein et al, Frankenburg, and Coppen and Bolander-Gouaille for discussions of the homocysteine hypothesis of depression.) According to Folstein et al, “The homocysteine hypothesis for depression, if true, would mandate inclusions of imaging studies for cerebrovascular disease and measures of homocysteine, folate, B12, and B6 in the clinical evaluation of older depressed patients.”

Omega-3 Fatty Acids

Evidence suggests that a significant inverse relationship exists between prevalence of major depression and annual consumption of fish, the prime source for 2 key omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). Patients with major depressive disorder exhibit lower levels of omega-3 fatty
acids than controls, and there are relationships within these populations between severity of depressive symptoms and lower plasma levels of omega-3 fatty acids. In addition, the ratio between omega-6 and omega-3 fatty acids in the diet may influence the proinflammatory response to stressors, and high omega-6–omega-3 ratios may enhance the risk for both depression and inflammatory diseases.

In 2006, Freeman et al. participated in a consensus conference on the role of omega-3 fatty acid treatment in psychiatric disorders (the conference was convened under the auspices of the Committee on Research on Psychiatric Treatments of the American Psychiatric Association). After an exhaustive examination of the evidence, the committee concluded that “the preponderance of epidemiological and tissue compositional studies supports a protective effect of omega-3 essential fatty acid intake, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in mood disorders.” Table 6.1 provides clinical recommendations for omega-3 fatty acids from the American Psychiatric Association.

Biological mechanisms that may explain the impact of omega-3 fatty acids in psychiatric disorders include:

- Increased serotonergic neurotransmission
- Alterations in dopaminergic function
- Regulation of CRH
- Inhibition of protein kinase C
- Suppression of phosphatidylinositol-associated second messenger activity
- Modulation of heart rate variability via vagal mechanisms
- Increased dendritic arborization and synapse formation
- Prevention of neuronal apoptosis
- Improved cerebral blood flow
- Regulation of gene expression
- Competition of EPA with arachidonic acid for enzymatic action and resultant reduction of the inflammatory response

Of the four RCTs that have been conducted to date, three have reported significant improvement in the treatment of depression after omega-3 fatty acid supplementation compared with nonsupplemented controls. The successful trials utilized either 98% pure ethyl ester EPA without DHA or a combination of EPA and DHA as an adjunctive treatment for antidepressant-refractory major depressive disorder. Dosages used were 1 g/d to 2 g/d of EPA alone or a higher dose in combination with DHA (9.6 g/d total). Treatment responses were rapid (as little as 2 weeks), effect sizes were large, and no significant adverse side effects were reported.

In studies of the effects of fish oil on other forms of depression, results have been inconsistent for bipolar disorder, and a lack of effect has been found for perinatal disorder. Studies to date have not supported the use of DHA alone or of alpha-linolenic acid as an intervention in psychiatric disorders.

Magnesium

Magnesium affects all elements of the HPA axis—it can suppress hippocampal kindling, reduce the release of ACTH, and affect adrenocortical sensitivity to ACTH. A 2002 review discussed magnesium’s involvement in the pathophysiology of depression:

“The role of magnesium in the central nervous system could be mediated via the N-methyl-D-aspartate-antagonistic, gamma-aminobutyric acid-agonistic or angiotensin II-antagonistic property of this ion. A direct impact of magnesium on the function of the transport protein p-glycoprotein at the level of the blood-brain barrier has also been demonstrated, possibly influencing
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the access of corticosteroids to the brain. Furthermore, magnesium dampens the calciumion-protein kinase C related neurotransmission and stimulates the Na-K-ATPase."187

Table 6.1—Omega-3 Fatty Acid Subcommittee, Recommendations Committee on Research on Psychiatric Treatments, The American Psychiatric Association182

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tr>
<td>All adults should eat fish ≥ 2 times per week.</td>
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<tr>
<td>Patients with mood, impulse-control, or psychotic disorders should consume 1 g EPA + DHA per day. A supplement may be useful in patients with mood disorders (1–9 g per day). Use of &gt; 3 g per day should be monitored by a physician.</td>
</tr>
<tr>
<td>Adapted from the American Heart Association recommendations to provide guidelines on omega-3 fatty acid use in the context of treating psychiatric disorders</td>
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Many studies have shown that magnesium deficiency induces depression- and anxiety-like behavior in rats and mice.188 Furthermore, magnesium reduced the immobility time in a forced swimming test, suggesting antidepressant effects.189, 190 In a 2005 experiment, magnesium doses ineffective per se given jointly with ineffective doses of imipramine resulted in a potent reduction in immobility time.191 Involvement of the NMDA/glutamate pathway was suggested by antagonism of magnesium-induced antidepressant-like activity by NMDA, as well as significant reduction of immobility time induced by a combination of ineffective doses of both NMDA antagonists and magnesium.

In humans, significantly lower serum magnesium levels have been found among depressed vs. control diabetic patients.192 “Magnesium treatment is hypothesized to be effective in treating major depression resulting from intraneuronal magnesium deficits. These magnesium ion neuronal deficits may be induced by stress hormones, excessive dietary calcium as well as dietary deficiencies of magnesium.” Rapid recovery (less than 7 days) from major depression using 125 to 300 mg of magnesium (as glycinate and taurinate) with each meal and at bedtime has been shown.193

Vitamin D

While the classic function of vitamin D is to regulate calcium homeostasis and thus bone formation and resorption, we now know that Th1 and Th2 cells are direct targets of the active form, 1,25-dihydroxy vitamin D3, which has been shown to inhibit the development of autoimmune diseases such as inflammatory bowel disease.194 Vitamin D- or vitamin D receptor-deficient rats have elevated Th1 cell-associated cytokine production and decreased Th2 cell IL-4 secretion. In addition, vitamin D has a neuroprotective role in hippocampal cell survival and may mitigate processes related to cellular homeostasis, possibly through a calcium-buffering mechanism.195 Other biological effects include synthesizing neurotrophic factors and at least one enzyme involved in neurotransmitter synthesis, inhibiting the synthesis of inducible nitric oxide synthase, and increasing glutathione levels, suggesting a role for the hormone in brain detoxification pathways. Low levels of vitamin D have been associated with mood disorders in the elderly.196

A 2007 review article by Michael Holick,197 one of the world’s experts on vitamin D, mentions the association between vitamin D deficiency and mood disorders. His treatment recommendation for vitamin D deficiency is “50,000 IU of vitamin D2 every wk for 8 weeks; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml. The goal is to achieve concentrations of 25-hydroxyvitamin D at about 30 to 60 ng per milliliter.” Unfortunately, there have been no RCTs of vitamin D as a primary treatment for diagnosed depression; a MESH search linking depression, treatment, and vitamin D on PubMed turned up only 5 citations, and all but 2 were published prior to 2000. Of those two, one was an RCT of women 70 years old or more (not diagnosed with depression), supplemented with 800 IU of vitamin D plus calcium, in which the treatment arm “did not lead to an improvement in mental health scores.”198 The other was a very small study (15 subjects) of short duration (1 month) comparing vitamin D therapy (100,000 IU) with phototherapy for SAD; all subjects receiving vitamin D improved in all outcome measures, while those receiving phototherapy showed no significant improvement.199 Clearly, the scientific community needs to explore this issue in far greater depth because vitamin D is intricately linked to many other chronic diseases that are also associated with
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depression (osteoporosis, cardiovascular disease, multiple sclerosis, and others\textsuperscript{97}). It seems a reasonable hypothesis that an underlying vitamin D deficiency (or significant insufficiency) may be one of the web-like interconnections contributing to both emotional and physical dysfunction.

Zinc

Zinc is present in particularly large concentrations in the mammalian brain, and several studies have found lower serum zinc levels in subjects suffering from major depression vs. non-depressed controls.\textsuperscript{200-203} A 2006 study found lower levels of zinc in postpartum depression.\textsuperscript{204} Low levels of zinc are associated with both markers of the inflammatory response (e.g., increased CD4+/CD8+ T cell ratio, serum neopterin, increased serum IL-6) and treatment-resistant depression.\textsuperscript{205-207} However, it is also well established that zinc deficiency impairs some aspects of immunity, indicating a more complex role in the mechanism of psychopathology and treatment of depression.\textsuperscript{207} Low serum zinc in depression may be secondary to both lower albumin and “sequestration of metallothionein in the liver, which may be related to increased production of IL-6.”\textsuperscript{208} Animal data strongly suggest antidepressant activity of zinc, and a preliminary placebo-controlled, double-blind pilot study of zinc supplementation in antidepressant therapy showed significantly reduced symptoms in patients with major depression after 6 and 12 weeks.\textsuperscript{209} Possible mechanisms\textsuperscript{207} for the antidepressant activity of zinc include: (1) direct antagonism of the NMDA receptor,\textsuperscript{210} (2) antagonism of group I metabotropic glutamate receptors\textsuperscript{211} or potentiation of AMPA receptors,\textsuperscript{212} both of which may attenuate the NMDA receptor function, or (3) direct inhibition of glycogen synthase kinase-3β.\textsuperscript{213}

Other Nutrients

Chromium — A placebo-controlled, double-blind pilot study found promising antidepressant effects of 600 µg/d of chromium picolinate; 70% of the patients with atypical depression taking the chromium and none of the patients taking placebo met responder criteria.\textsuperscript{214} In a more recent double-blind multicenter trial, the same dose of chromium picolinate reduced carbohydrate cravings and regulated appetite in a population of adults with atypical depression, most of whom were overweight or obese.\textsuperscript{215} Chromium also improved diabetic rats’ performance in forced swimming tests, with involvement of serotonergic pathways and potassium channels.\textsuperscript{216}

Iron — Mean ferritin levels were significantly lower in depressed vs. nondepressed students in a 2007 case-control study,\textsuperscript{217} but another study looking at 6 parameters of iron metabolism and mild depressive symptoms in an older population did not find a similar association.\textsuperscript{218} Infants with iron deficiency anemia test lower in cognitive, motor, social-emotional, and neurophysiological development than comparison group infants. According to a 2006 review,\textsuperscript{219} iron therapy does not consistently improve developmental outcome, but randomized trials of infant iron supplementation have shown benefits, indicating that adverse effects can be prevented and/or reversed with iron earlier in development or before deficiency becomes severe or chronic.

Selenium — Selenium status may modify mental function. “Glutathione peroxidase, thioredoxin reductases, and one methionine-sulfoxide-reductase are selenium-dependent enzymes involved in antioxidant defense and intracellular redox reduction and modulation. Selenium depletion in animals is associated with decreased activities of selenium-dependent enzymes and leads to enhanced cell loss in models of neurodegenerative disease.”\textsuperscript{220} A 2002 article suggested that the improvement in depressed alcoholics after a period of abstinence from alcohol might be in part related to the coinciding normalization of selenium status.\textsuperscript{221} In an earlier article, the same author observed that selenium is required for appropriate thyroid hormone synthesis, activation, and metabolism and that selenium deficiency decreases immunocompetence and promotes viral infections, possibly providing a link between depression, hypothyroidism, and increased susceptibility to viral infection.\textsuperscript{222}

Iodine — The offspring of iodine-deficient rats had significantly reduced blood supply to the dorsal hippocampus and cerebellar cortex, as well as loss of the ability to learn, in 2 recent studies.\textsuperscript{223, 224} Addition of iodine to the diet
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