CHAPTER 8

Trauma and Medically Unexplained Symptoms

MYSTERIOUS MEDICAL ILLNESSES

Medically unexplained symptoms (MUS) are generally defined in the mainstream medical literature as numerous and varied somatic complaints for which conventional biomedical explanations cannot be provided by examination or further investigation. This definition addresses a lack of knowledge and seems neutral in tone. Less neutral, more strident definitions characterize MUS as physical symptoms having little or no basis in underlying organic disease, manifestations of emotional disorders. Recent articles in medical journals continue to recommend psychotherapy and psychopharmacological treatment, with a focus on functional improvement rather than symptom reduction.

These symptoms have been described and categorized into a group of syndromes, which include fibromyalgia, rheumatoid arthritis (RA), reflex sympathetic dystrophy (RSD), Hashimoto’s thyroiditis, Graves’ disease, systemic lupus erythematosus (SLE), Sjögren’s syndrome, Crohn’s disease, type 1 diabetes, multiple sclerosis (MS), and chronic fatigue syndrome (CFS). The list continues to grow, yearly.

Fortunately, as we shall see, these diseases appear to be explainable. As in other issues that we have already explored, the full details of the problem may not be evident, but the contours are apparent and inferable. The central character in this mystery appears to be the steroid cortisol, whose relationship to trauma and these diseases has been puzzling and bewildering, owing mainly to faulty empirical methodologies in its collection, extraction, measurement, and analysis. In order to understand these seemingly enigmatic medical conditions, we need to appreciate the relationships between the autonomic, endocrine, and immune systems, specifically focusing on cortisol’s role in their interrelated functioning.
The Autonomic Nervous System

Recall that, in contrast to the central nervous system, comprised of the brain and spinal cord, the autonomic nervous system (ANS) is the part of the peripheral nervous system that acts as a control structure, functioning largely below the level of consciousness and controlling visceral (organ) functions. The ANS affects heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, micturition (urination), and sexual arousal. Whereas most of its actions are involuntary, some, such as breathing, work in tandem with the conscious mind.

Divisions of the ANS

Recollect also that the ANS is traditionally divided into two subsystems, the parasympathetic nervous system and sympathetic nervous system. The sympathetic division is energy expanding and arousal mediating. The parasympathetic division is energy conserving, homeostatic, and calm mediating. The sympathetic and parasympathetic divisions typically function in opposition to each other, though this opposition is better conceptualized as complementary in nature rather than antagonistic. As an analogy, one may think of the sympathetic division as the accelerator and the parasympathetic division as the brake. Hence, we can view the sympathetic branch as mediating “approach, seek, fight, or flight” and the parasympathetic branch as “rest and digest” and/or freeze (Dodd & Role, 1991).

Neural signaling within the two branches is mediated by neurotransmission. The sympathetic branch is catecholamine mediated, utilizing, predominantly, norepinephrine/noradrenaline, epinephrine/adrenaline, and dopamine. The parasympathetic branch is generally cholinergically mediated, utilizing acetylcholine transmission.

The Endocrine System

The endocrine system is a system of glands, each of which secretes a type of hormone as a chemical messenger directly into the bloodstream to regulate the body. The endocrine system contrasts with the exocrine system, which secretes its chemical messengers utilizing ducts, and the ANS, which utilizes neurotransmitters as chemical messengers. Its name derives from the Greek words endo (inside, within) and crinis (secretion). The endocrine system is an information signaling system, like the nervous system, yet its effects and mechanism are classifiably different. The endocrine system’s effects are slow to initiate and prolonged in their response, lasting for hours to weeks. The nervous system sends information very quickly, generally over short distances, and responses are generally short lived. Hormones are the chemical messengers released from endocrine tissue into the bloodstream where they travel, often long distances, to target tissue and generate a response. Hormones regulate various human functions, including metabolism, growth and development, tissue function, and mood (Kupfermann, 1991a).

The Integration of ANS and Endocrine Systems

The ANS and endocrine system join to form metabolic pathways or axes. Sympathetic mediation is carried out by the functioning of the sympathoadrenomedullary (SAM) axis, wherein the adrenal medulla (on the kidneys) generates the production of the hormone epinephrine and, in combination with brainstem areas (locus caeruleus), the production of norepinephrine. When mediated by the adrenal medulla, norepinephrine is secreted as a hormone. When mediated by the locus caeruleus, it is produced as a neurotransmitter. Recall from Chapter 3 that hormones and neurotransmitters function as chemical messengers. Hence, the SAM axis is considered to be neuroendocrine, consisting of neural and endocrine tissue (Kupfermann, 1991a).

In contrast, parasympathetic function is mediated predominantly through endocrine function. The glandular mediation of the endocrine system is, generally, carried out by the hypothalamus, pituitary, and adrenal glands. These glands signal each other sequentially and are therefore considered to form and function as an axis, the hypothalamic-pituitary-adrenal (HPA) axis (Kupfermann, 1991a).

The HPA Axis and Cortisol

The HPA axis can be activated for various reasons but predominantly by the sleep/wake cycle, during stress, and for immune function. This axis functions as a complex set of direct, sequential influences and feedback interactions among the hypothalamus, the pituitary (a pea-shaped structure located below the hypothalamus), and the adrenal (or suprarenal) glands (small, conical organs on top of the kidneys).

So, for example, when the HPA axis is activated, the hypothalamus mediates the secretion of corticotropin-releasing factor (CRF)/corticotropin-releasing hormone (CRH), which then signals the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), in turn signaling the adrenal cortex to secrete cortisol. When the appropriate level of cortisol is reached, its presence initiates a negative feedback on the hypothalamus and pituitary, mediating the inhibition of further CRF/CRH and ACTH production, thereby curtailing further cortisol production (Engelmann, Landgraf, & Woljak, 2004). We will return to this.

The Immune System

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by "foreign" invaders. These invaders are primarily microbes, tiny organisms such as bacteria, parasites, fungi, and viruses that can cause infections. The human body provides an ideal environment for many microbes. It is the immune system’s function to keep them out or, failing that, to seek out and destroy them. In addition, the
immune system functions to prevent cell mutations, collectively referred to as tumors or cancers. The immune system is amazingly complex. It can recognize and remember millions of different enemies, and it can produce secretions (release of fluids) and cells to match up with and wipe out nearly all of these microbes. The secret to its success is an elaborate and dynamic communications network. Millions of cells organized into sets and subsets gather like clouds of bees swarming around a hive and pass information back and forth in response to an infection. Once immune cells receive the alarm, they become activated and begin to produce powerful chemicals referred to as antibodies. These substances allow the cells to regulate their own growth and behavior, to enlist other immune cells, and to direct them to infectious trouble spots. Under normal conditions, the immune system is able to launch attacks that destroy invading microbes, infected cells, and tumors, while ignoring healthy tissues and, when necessary, facilitating the protection and growth of cells (Male, Brostoff, Roth, & Roitt, 2006).

**Self Versus Nonself**

Normally, the key to a balanced immune system is its remarkable ability to distinguish between the body’s own cells, recognized as “self,” and foreign cells, recognized as “nonself.” The body’s immune defenses normally coexist with cells that carry distinctive self marker molecules. When immune defenders encounter foreign cells or organisms carrying markers that are identified as nonself, they quickly launch an attack. Anything that can trigger this immune response is referred to as an antigen. An antigen can be a microbe, such as a virus, or a part of a microbe, such as a molecule. Tissues or cells from another person (except an identical twin) also carry nonself markers and act as foreign antigens. That is why tissue transplants are, at times, rejected.

In some cases, the immune system responds to a seemingly harmless foreign substance, such as ragweed pollen. The result is an allergy, and this kind of antigen is referred to as an allergen. Immunoglobulin E (IgE), whose natural job is to protect against parasitic infections, is likely responsible for the symptoms of allergy. Immunoglobulin D (IgD) remains attached to B cells and plays a key role in initiating early B cell responses.

**Autoimmune Structure**

**Lymphocytes**

The organs of the immune system are positioned throughout the body. They are called lymphoid organs because they are home to lymphocytes, small white blood cells that are the key players in the immune system. Bone marrow, the soft tissue in the hollow center of bones, is the ultimate source of all blood cells, including lymphocytes. The thymus gland is another lymphoid organ. Lymphocytes known as T lymphocytes or T cells (T denotes the thymus) mature in the thymus and then migrate to other tissues. B lymphocytes, also known as B cells, become activated and mature into plasma cells, which make and release antibodies. Lymph nodes, which are located in many parts of the body, are lymphoid tissues that contain numerous specialized structures, such as T cells and B cells. Lymphocytes can travel throughout the body using the blood vessels. They can also travel through the system of lymphatic vessels that closely parallels the body’s veins and arteries (Male et al., 2006).

B cells and T cells are the main types of lymphocytes. B cells work chiefly by secreting substances called antibodies, such as immunoglobulins, into the body’s fluids. Antibodies ambush foreign antigens circulating in the bloodstream. They are powerless, however, to penetrate cells. The job of attacking and penetrating target cells, either cells that have been infected by viruses or cells that have been distorted by cancer, is left to T cells and other immune cells.

**Immunoglobulins**

Many of the B-cell-mediated antibodies created are immunoglobulins. Immunoglobulin G (IgG) is a type of antibody that works efficiently to coat microbes, speeding their uptake or absorption by other cells in the immune system. Immunoglobulin M (IgM) is very effective at killing bacteria. Immunoglobulin A (IgA) concentrates in body fluids, tears, saliva, and the secretions of the respiratory and digestive tracts, guarding the entrances to the body. Immunoglobulin E (IgE), whose natural job is to protect against parasitic infections, is likely responsible for the symptoms of allergy. Immunoglobulin D (IgD) remains attached to B cells and plays a key role in initiating early B cell responses.

**Microphages and Natural Killer T Cells**

In addition to lymphocytes, the immune system stockpiles a large arsenal of cell-devouring phagocytes/microphages and natural killer T cells (NKT cells). Some immune cells take on all intruders, whereas others are focused on highly specific targets. The immune system stores just a few of each kind of these different cells needed to recognize millions of possible enemies. When an antigen first appears, the few immune cells that can respond to it multiply into a full-scale army of cells. After their job is done, the majority of immune cells fade away, leaving a small number behind that function as sentries to watch for future attacks. In order to work effectively, immune cells need to work communicatively and systemically. At times, immune cells communicate by direct physical contact. Generally, though, they communicate through yet another class of chemical messengers, known as cytokines (Abbas, Lichtman, & Pillai, 2012). We revisit this in detail, below.
The Antiinflammatory–Inflammatory Balance

The immune system mediates a balance between antiinflammatory, neuroprotective, cell survival and growth, and inflammatory, neurotoxic, cell death (Allen & Rothwell, 2001; Rothwell, 1999; Szelenyi & Vizi, 2007). Therefore, an inflammatory shift in immune balance increases immune functions, whereas an antiinflammatory shift in balance decreases immune function.

The need for the inflammatory function is obvious, intended for our protection against illness and uncontrolled cell growth (tumors). On the other hand, our body also requires neural protection; at times, neural growth (synaptogenesis); and at other times, neural regeneration. We have already explored synaptogenesis in the context of our gestational and postpartum neural maturation, wherein our brain grows (in utero) and wires and rewires itself during our postpartum maturation and development. In addition, the growth requirements of our bodies necessitate the need for cell growth. We have also discovered, recently, that certain areas of the adult brain, such as the hippocampus, retain the ability to promote neural growth during learning and subsequent to psychotherapy. Indeed, neural plasticity, the central organizing force of consciousness, may very well require neural protection. Also, subsequent to injury to the body and brain, the healing process manifested by cell regeneration requires neural protection. All these functions require an antiinflammatory shift in balance. Also, during periods of acute traumatic stress, reduction in immune function is required to mediate the physiological needs of flight and/or flight neural systems. We will return to this area, below.

The HPA Axis, Cortisol, and the Immune Balance

It is at the neuroendocrine–immune interface that our central character, cortisol, emerges to facilitate the immune balance, one of cortisol’s main functions (Mastorakos, Karoutsou, & Mizamtsidi, 2006). Elevations of cortisol levels suppress immune function, whereas depressions of cortisol levels enhance immune function. Therefore, when there is a need for an antiinflammatory shift, the HPA axis is activated. As a result, the hypothalamus mediates the secretion of CRF/CRH, which then signals the anterior pituitary to secrete ACTH, in turn signaling the adrenal cortex to secrete cortisol. In this situation, the negative feedback on the hypothalamus and pituitary is reduced, allowing for an increased production of cortisol, thereby suppressing immune function. Conversely, when a need arises for an inflammatory shift, the negative feedback on the hypothalamus and pituitary is enhanced, thereby reducing cortisol levels and enhancing immune function.

Cytokines and Immunochemical Messaging

The orchestration of inflammatory and antiinflammatory responses is contingent on a system of communications between the immune cells (T cells, B cells, NKT cells, microphages) and a group of proteins, or glycoproteins, collectively referred to as cytokines (Allen & Rothwell, 2001; Rothwell, 1999; Szelenyi & Vizi, 2007). Cytokines belong to three families, generally referred to as interferons, interleukins, and tumor necrosis factors (TNFs).

Neurotoxic and neuroprotective mechanisms are closely related to the balance between the inflammatory and antiinflammatory cytokines, respectively. Hence, specific cytokines are expressed during human development, injury, and disease. Like cortisol, cytokines mediate immune function in both directions. Cytokines can be thought of as the generals of the immune army, thereby giving the orders for attack or for standing down and retreating. So, for example, when a need arises for an inflammatory shift in immune balance, cortisol levels are reduced, and inflammatory cytokine levels are enhanced, leading to the release of T cells, B cells, NKT cells, and microphages, which attack and destroy the nonself intruders. Conversely, when a need arises for an antiinflammatory shift in immune balance, cortisol levels are elevated, and antiinflammatory cytokine levels are enhanced, leading to the reduction of T cells, B cells, NKT cells, and microphages, resulting in an enhanced neuroprotective environment.

Cortisol, Immune Function, and Stress

When evolution began to tinker with our endocrine stress response thousands of years ago, stress was created by danger, not work, finances, the global economy, or any of our modern artifacts of stress induction. Consequently, stress was a situation that called for fight or flight mechanisms. From that perspective, nothing has changed our evolutionary neuroendocrine–immune response to the experience of stress.

So, if we reflect on a situation that calls for a flight or fight decision (attack, surviving a natural disaster, drowning, etc.), our neuroendocrine–immune response will be expressed as follows: (a) Our SAM axis will become activated, wherein the adrenal medulla (on the kidneys) will generate the production of epinephrine and, in combination with brainstem areas (locus caeruleus), the production of norepinephrine. These hormonal changes will facilitate an increase in blood sugars (glucose), blood pressure, and respiratory and metabolic rates. (b) Our HPA axis will become activated, wherein the hypothalamus will mediate the secretion of CRF/CRH, which will then signal the anterior pituitary to secrete ACTH, in turn signaling the adrenal cortex to secrete cortisol. The negative feedback on the hypothalamus and pituitary will be suppressed, thereby mediating enhanced cortisol production and an antiinflammatory immune balance. This hormonal change will facilitate an increase in blood volume and blood pressure, enhanced conversion of proteins and fats to glucose, and a reduction in immune function.

In situations of acute danger, these changes are adaptive, in that they mediate and fuel the usage of fight or flight options. Immune and digestive
functions are reduced owing to their intensive usage of fuel and energy, changes that are adaptive in the short term. According to evolution's blueprint, danger is generally not long term; you either escape or die. However, in modern times, and in the absence of a much-needed evolutionary upgrade, our manifestations of stress can be long term. Consequently, the prolonged maintenance of the endocrine changes and persistent unneeded inflammatory immune balance can eventually lead to hypertension, anxiety, gastrointestinal illness, impaired healing and immune function, heart disease, diabetes, and cancers.

The Enigma of Cortisol and Posttraumatic Stress Disorder

The data from investigations of the neuroendocrinology of posttraumatic stress disorder (PTSD) have evidenced alterations that have not historically been associated with disorders of stress. Rachel Yehuda (2006) opines that the most "infamous" of these observations, lowered cortisol levels, has been the subject of much scrutiny because the finding has been counterintuitive and not uniformly reproducible.

High cortisol levels have historically been linked with stress, so much so that in the human and animal literature, the magnitude of the stress has often been defined by the level of cortisol secreted (Yehuda, 1997). Hence, high levels of cortisol secretion have been considered the de facto evidence that stress has occurred. As a result of this strong association between cortisol levels and stress and depression, it was initially hypothesized that cortisol levels would be elevated in PTSD. However, the first exploration of cortisol levels in PTSD demonstrated that the 24-hour urinary excretion of cortisol was actually lower in combat veterans with PTSD as compared to hospitalized patients with other psychiatric diagnoses such as major depression, schizoaffective disorder, bipolar disorder, and schizophrenia (Mason, Giller, Kosten, Ostroff, & Harkness, 1986). For the next few years, four of six cortisol studies verified these findings, suggesting a unique endocrine signature for PTSD.

Since then, however, several hundred peer-reviewed journal articles reporting on various aspects of HPA function in subjects with PTSD have been published, with results that have done more to confuse the issue than offer any enlightenment. These findings have indicated cortisol elevations, depressions, and nondifferences. Even in more refined methodological examinations of cortisol, spanning multiple measurements over 24 hours, the results have been mixed. Thus, when compared to controls, ambient cortisol findings for subjects with PTSD over 24 hours were found to be lowered, elevated, and insignificant (see Yehuda, 2002, 2006 for excellent reviews and discussion). Consequently, these findings have raised the question as to whether cortisol levels have any meaning. As we shall see in what follows, examining briefly the methods of collection, extraction, measurement, and analysis of cortisol will facilitate an understanding of these seemingly disparate findings.

Methodological Inconsistency

Rachel Yehuda (2006) argues that methodological details regarding how cortisol levels were ultimately obtained are given surprisingly little attention in the PTSD literature. Although methodological issues regarding age, sex, height, weight, and menstrual status have been focal of discussion, what have been neglected are the details regarding the collection, extraction, measurement, and analysis of cortisol. The reader is referred to this article for a detailed exploration and discussion.

Yehuda (2006) notes that the fewest methodological problems are likely to result from cortisol assayed from blood samples and from measurements taken throughout the day. Yehuda maintains that cortisol levels that were measured from a single blood draw are not generally thought to provide reliable measurements of ambient (throughout the day) levels, given that many artifacts, such as stress and varied sleep cycles, could create artificial elevations of cortisol, leading to the wide range of findings. In addition, the use of repetitive venous puncture rather than an indwelling catheter (inserted once) could easily produce cortisol spikes due to even a minor unpleasantness.

Salivary samples, Yehuda (2006) notes, could have been contaminated with food particles. With urine samples, there was the additional problem of insuring completeness of collections if subjects were asked to collect samples at home. Home sampling was also problematic because it was impossible to ensure that subjects had adhered to the protocol with respect to collection times (for saliva), completeness of collection (for urine), as well as dietary or exercise restrictions. Additionally, extraction procedures, markedly more complex than with blood plasma, allowed for more error and the resultant discrepancies.

Posttraumatic Stress Disorder and Hypocortisolemia

When properly done, cortisol investigations in persons with PTSD have revealed consistent findings of hypocortisolemia (depressed cortisol levels). The reader is referred to Yehuda (2002 and 2006) for reviews and discussion of these studies. Cortisol levels in persons with PTSD were found to be reduced when compared to cortisol levels in those with depression and/or control subjects. Cortisol levels were found to be lower in subjects with PTSD as compared to controls and in combat veterans with PTSD as compared to controls and combat veterans without PTSD. Similar findings of hypocortisolemia were found in children who survived the 1988 earthquake in Armenia, exhibiting posttraumatic reactions 5 years after the fact. Findings of cortisol suppression were found in female adult survivors of childhood sexual abuse, as compared to controls. Finally, findings of hypocortisolemia were found in Gulf War combat veterans with intrusive posttraumatic symptoms, holocaust survivors (in excess of 50 years of the holocaust), and aging combat veterans, as compared to controls.
Subjects with PTSD and Their Offspring

Offspring of holocaust survivors (with PTSD) evidenced significantly lower cortisol excretion than offspring of holocaust survivors without PTSD symptoms. This was found to be true whether or not the offspring exhibited any PTSD symptoms. The reader is referred to Yehuda, Teicher, et al. (2007) for a listing and discussion of these studies.

In a most striking study, Yehuda, Engel, Brandt et al. (2005) reported findings of low cortisol levels in mothers who developed PTSD in response to exposure to the World Trade Center attack and collapse of September 11, 2001, and their 1-year-old babies, as compared to mothers who did not evidence PTSD in response to the attacks and their babies. With this study, we have our first evidence that hypocortisolism can be caused by glucocorticoid (cortisol) programming in utero. Because not all children born to mothers with PTSD will necessarily develop PTSD, this finding underscores the fact that hypocortisolism can also manifest in a population without PTSD population. We will return to the questions and possible implications of this finding, below.

What appears to be clear from the foregoing is that PTSD does have a unique endocrine signature and that this endocrine profile must have direct and profound implications on immune function. Recall that elevations of cortisol levels suppress immune function, whereas depressions of cortisol levels enhance immune function. However, in the case of PTSD, or in offspring (of PTSD sufferers), wherein the offspring do not manifest PTSD, cortisol suppression is not induced by immune needs, thereby creating the potential for an inflammatory, hyperimmune balance, in the absence of bacterial, viral, fungal, parasitic, or carcinogenic invasion.

Medically Unexplained Symptoms

As we noted above, these symptoms have been described and categorized into a group of syndromes, which include fibromyalgia, RA, RSD, Hashimoto’s thyroiditis, Graves’ disease, SLE, Sjögren’s syndrome, Crohn’s disease, type 1 diabetes, MS, and CFS.

In the absence of methodological flaws or inconsistencies, the studies of MUS consistently point at hypocortisolism. The reader is referred to Bohmelt, Nater, Franke, Hellhammer, and Ehlert (2005) and Heim, Ehlert, and Hellhammer, (2000) for reviews and discussions of these studies. Hence, there is considerable evidence for decreased adrenal activity and reactivity manifested in decreased cortisol output in patients with a myriad of bodily disorders. These disorders have been related to stress or trauma experience, and there seems to be considerable symptom overlap among these disorders (Heim et al., 2000), suggesting a spectrum of related diseases with similar neuroendocrine correlates.

If hypocortisolism is central to these diseases, an examination should reveal consistent findings of inflammatory cytokines and the resultant lymphocytes and antibodies in the areas affected by these illnesses. Additionally, consistent findings of inflammatory cytokines are consistent with the chronic pain that many of these diseases manifest with (for reviews, see Watkins & Maier, 2000, and Dantzer, 2005).

Sjögren’s Syndrome

Sjögren’s syndrome manifests as an autoimmune disorder in which the body’s immune system mistakenly reacts to the tissue in glands that produce moisture, such as tear and salivary glands. It is a chronic inflammatory disease that can progress to a more complex systemic disorder that affects other tissues and organs in the body, such as joints, kidneys, and the intestinal tract.

Sjögren’s syndrome is characterized by an unusual accumulation and infiltration of a particular type of antibody and/or lymphocyte in the glands that are responsible for fluid production (see Witte, 2005, for a review of such studies). Specifically, these antibodies (antifodrin and ant centromere) function as autoantibodies, given that they attack healthy tissue, not infectious invasion. Consequently, the amount and quality of saliva and tears produced decreases with Sjögren’s syndrome, leading to a characteristic dry mouth and dry eyes, which are referred to as sicca syndrome. Other mucous membranes may also dry out. Those with this condition often have a feeling of sand or grit in their eyes, swollen salivary glands, difficulty swallowing, and a decreased sense of taste. The diagnosis is derived either from blood-work investigations of antibodies or cytokines or from biopsies investigating the presence of antibodies in glandular areas.

The disorder may present as primary Sjögren’s syndrome or as secondary Sjögren’s syndrome, wherein the condition coexists with other autoimmune disorders, such as SLE, polymyositis, scleroderma, or RA. Most of the complications of Sjögren’s syndrome occur because of decreased tears and saliva. Consequently, people with dry eyes are at increased risk for infections around the eye and may have damage to the cornea. Dry mouth may cause an increase in dental decay, gingivitis (gum inflammation), and oral yeast infections (thrush), which may cause pain and burning. Some people have episodes of painful swelling in the salivary glands around the face. Complications in other parts of the body can occur. Pain and stiffness in the joints with mild swelling may occur in some people, even in those without RA or lupus. Rashes on the arms and legs related to inflammation in small blood vessels (vasculitis) and inflammation in the lungs, liver, and kidney may occur rarely and be difficult to diagnose. Numbness, tingling, and weakness also have been described in some people.

Hashimoto’s Thyroiditis

Hashimoto’s thyroiditis, also referred to as chronic lymphocytic thyroiditis, is an autoimmune disease in which the thyroid gland is gradually infiltrated
by a variety of autoantibody-mediated immune processes (see McLachlan & Rappaport, 1992, and Legakis, Petroianii, Saramantis, & Tolis, 2001, for reviews). It was the first disease to be recognized as an autoimmune disease. Hashimoto’s thyroiditis very often results in symptoms of hypothyroidism. Hashimoto’s thyroiditis, as an autoimmune disease, is differentiated from hypothyroidism, a symptomatic condition without autoantibody infiltration.

Physiologically, antibodies against thyroid peroxidase and/or thyroglobulin cause gradual destruction of follicles in the thyroid gland. Accordingly, the disease can be detected clinically by looking for these antibodies in the blood. Hence, Hashimoto’s thyroiditis is characterized by invasion of the thyroid tissue by leukocytes, mainly T lymphocytes. Symptomatically, every organ system slows in function. Consequently, the brain slows down, making it difficult to concentrate. The gut slows down, causing constipation, and metabolism slows down, causing weight gain, fatigue, and depressive symptoms.

Graves’ Disease

Graves’ disease is an autoimmune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism). Graves’ disease is also the most common cause of severe hyperthyroidism that is accompanied by more clinical signs and symptoms and laboratory abnormalities as compared with milder forms of hyperthyroidism (Iglesias, Dëvora, et al., 2009).

In Graves’ disease, the immune system produces antibodies called thyroid-stimulating immunoglobulin. These antibodies bind/attach to the thyroid-stimulating hormone receptors, which are located on the cells that produce thyroid hormones in the thyroid gland (follicular cells) and chronically stimulate them, resulting in an abnormally high production of thyroid hormones (Saravanan & Dayan, 2001). This causes the clinical symptoms of hyperthyroidism and the enlargement of the thyroid gland (visible as a goiter). Approximately 25% to 30% of people with Graves’ disease will also have Graves ophthalmopathy, a protrusion of one or both eyes caused by inflammation of the eye muscles by attacking autoantibodies. Other autoantibodies, thyroid growth immunoglobulins and thyrotropin-binding inhibitory immunoglobulins have, also, been observed. Still other observations have reported infiltrations of B and T lymphocytes (Wang, Chen, et al., 2007).

Graves’ disease can exhibit a variety of symptoms related to hyperthyroidism, including diffuse goiter (enlarged thyroid gland), rapid pulse, weight loss, and trembling. In addition, some people with Graves’ disease exhibit symptoms unique to this form of hyperthyroidism, including ophthalmopathy (bulging eyes) and, rarely, pretibial myxedema (swelling of shins). The symptoms of Graves’ disease stem partly from hyperthyroidism and partly as a consequence of autoimmune self-attack.

Fibromyalgia

Derived from the Latin *fibro-* (fibrous tissues) and Greek *myo-* (muscle) and *algos-* (pain), fibromyalgia manifests as muscle and connective tissue pain and a heightened painful response to slight or moderate pressure. Other symptoms may include tingling of the skin, prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, and palpitations. Although fibromyalgia is classified based on the presence of chronic widespread pain, pain may also be localized in areas such as the shoulders, neck, lower back, hips, or other areas.

Other symptoms often attributed to fibromyalgia that may possibly be due to comorbid (co-occurring) disorders include the following: myofascial pain syndrome, diffuse nondermatomal paresthesias, functional bowel disturbances and irritable bowel syndrome, genitourinary symptoms and interstitial cystitis, dermatological disorders, headaches, myoclonic twitches, and symptomatic hypoglycemia. Twenty to thirty percent of patients with RA and SLE may also have fibromyalgia (Yanus, 2007).

An immunoinflammatory profile is supported by studies reporting elevated levels of proinflammatory cytokines (Maes et al., 1999; Thompson & Barkhuizen, 2003). Additional evidence for immune activation in fibromyalgia is provided by observations of increased NKT cells and T-lymphocyte autoantibodies (Fries, Hesse, Hellhammer, & Hellhammer, 2005).

Crohn’s Disease

Crohn’s disease presents as an inflammatory disease of the intestines that may affect any part of the gastrointestinal tract, causing a wide variety of symptoms. It primarily causes abdominal pain, diarrhea (which may be bloody if inflammation is at its worst), vomiting, or weight loss. It may also cause complications outside the gastrointestinal tract, such as rashes, arthritis, inflammation of the eyes, tiredness, and lack of concentration. Also referred to as inflammatory bowel disease, it typically manifests in the gastrointestinal tract and can be categorized by the specific tract or region affected. It can affect both the ileum (the last part of the small intestine, which connects to the large intestine) and the colon (the large intestine). Ileocolic Crohn’s disease accounts for 50% of cases. Crohn ileitis, manifested in the ileum only, accounts for 30% of cases, whereas Crohn colitis, of the large intestine, accounts for the remaining 20% of cases and may be particularly difficult to distinguish from ulcerative colitis (Baumgart & Sandborn, 2007).

Crohn’s disease manifests as an autoimmune disease, with inflammation stimulated by an overactive inflammatory cytokine and resultant varied T-cell and autoantibody response (Cobrin & Abreu, 2005; Elson et al., 2007). Similar observations of high levels of the cytokine TNF-alpha have been associated with the development of intestinal inflammation in Crohn’s disease (Behm & Bickston, 2008).
**Systemic Lupus Erythematosus**

Systemic lupus erythematosus is a systemic autoimmune disease or autoimmune connective tissue disease that can affect any part of the body. As occurs in other autoimmune diseases, the immune system attacks the body's healthy cells and tissue, resulting in inflammation and tissue damage. It is a hypersensitivity reaction caused by antibody-immune complex formations. Systemic lupus erythematosus most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. The course of the disease is unpredictable, with periods of illness (called *flares*) alternating with remissions (see Rahman & Isenberg, 2008, for a review).

Autoantibodies, such as antinuclear antibodies, seen in systemic lupus are directed against nuclear antigens such as nucleosomes, DNA, and histone proteins found within the body's cells and plasma. Hence, these autoantibodies are involved in the development of the disease, either by forming immune complexes that lodge in target organs, disrupting normal organ function, or by cross-reacting with targeted antigens and damaging tissue. Put another way, the systemic aspect of this disease is driven by the fact that these antibodies attack the cell, systemically, by attacking the nucleus and DNA. Further systemic damage is achieved by the fact that the cells of any organ system can be targeted, as opposed to specific organ systems such as those attacked in Hashimoto's thyroiditis, Graves' disease, or Crohn's disease.

**Rheumatoid Arthritis**

Rheumatoid arthritis is a chronic, systemic inflammatory disorder that may affect many tissues and organs but principally attacks the joints. The process produces an inflammatory response of the synovium (a lubricating fluid within the joint), secondary to hyperplasia (a marked growth in cell numbers) of synovial cells, resulting in excess synovial fluid and the development of pannus (an abnormal type of fibrovascular tissue that grows in a cancer-like fashion) in the synovium. The pathology of the disease process often leads to the destruction of cartilage and the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, heart, pleura (cavity surrounding the lungs), and sclera (the white area of the eye) as well as nodular lesions, most common in subcutaneous (below the skin) tissue.

Rheumatoid arthritis typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful, and stiff, particularly early in the morning on waking or following prolonged inactivity. As the pathology progresses, the inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to marked deformity.

Rheumatoid factor autoantibodies (created by B cells) and T cells have been detected in the majority of patients with the established disease, as have another group of autoantibodies, including antiperinuclear factor, antikeratin, and antiflaggrin autoantibodies (De Rycke et al., 2004). These antibodies are themselves thought to be antibodies created by IgM and IgG, which have been found consistently in investigations of RA (Sherer et al., 2005). Regardless of the specifics of the autoantibodies produced, RA clearly manifests as an autoimmune disease.

**Type 1 Diabetes**

Type 1 diabetes mellitus (also known as Type 1 diabetes or juvenile diabetes) is a form of diabetes mellitus, appearing typically in adolescence, that results from autoimmune destruction of the insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms of Type 1 diabetes include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), fatigue, and weight loss (Cooke & Plotnick, 2008). Although presenting typically in adolescence, it may present at earlier or later ages.

The process that appears to be most common is an autoimmune response (attack) toward insulin-producing beta cells involving an expansion of autoreactive T cells, autoantibody-producing B cells, and in general, the activation of the innate immune system (Bluestone, Herold, & Eisenbarth, 2010). Accordingly, examination of the pancreas reveals infiltration by T lymphocytes and B-cell-produced autoantibodies. By definition, the diagnosis of Type 1 diabetes can be made first at the appearance of clinical symptoms and/or signs. However, the finding of lymphocytes and autoantibodies is the cornerstone of a proper diagnosis. On the other hand, findings of these autoantibodies can occur prior to typical diabetic symptoms and is referred to as latent autoimmune diabetes.

**Reflex Sympathetic Dystrophy—Complex Regional Pain Syndrome**

Reflex sympathetic dystrophy, also called complex regional pain syndrome (CRPS), is a chronic progressive disease characterized by severe pain, swelling, and changes in the skin. Other clinical signs include edema and disturbed blood flow to the skin. These alterations of evoked pain sensitivity and swelling are not restricted to single or specific peripheral neural territories and are often disproportionate in severity to the precipitating injury. In other words, the symptoms of CRPS usually manifest near the site of an injury, which is usually minor. The most common symptoms overall are burning and electrical-like sensations, described to be like "shooting pain." People also experience muscle spasms, local swelling, abnormally increased sweating, changes in skin temperature (usually hot but sometimes cold), changes to skin color (bright red or a reddish violet), softening and thinning of bones, joint tenderness or stiffness, hair loss or hair growth, and/or restricted or painful movement.
Recently, research regarding increased inflammatory immune processes in the mediation of RSD/CRPS has become clearer (see Huygen, Bruijn, Klein, & Zijlstra, 2001, and Watkins & Maier, 2005, for reviews). In particular, inflammatory cytokines, such as TNF-alpha and interleukin-6, have been shown to be involved in the mediation of the pain. In some cases, these cytokines were also found externally, in affected skin blisters. Therefore, we have further evidence that although immune processes are highly adaptive when directed against pathogens or cancer cells, they can also come to be directed against the peripheral nervous system.

Most cases of RSD or CRPS originate in areas previously involved in unremarkable or noncomplex injuries, such as bruises, strains, or noncomplex fractures. In many of these injuries, minor damage is incurred by neurons, particularly to the myelin, the neural insulation around the axon. This releases neural proteins that are normally encased and hidden within the myelin sheath (Watkins & Maier, 2005). Under normal circumstances, this poses no problem. However, in an environment of hypocortisolemia and its resultant inflammatory immune balance, these harmless neuroproteins are now responded to as nonself by inflammatory cytokines, such as TNF-alpha and interleukin-6, triggering the attack of T cells, microphages, and B cell antibodies. This immune attack of peripheral nerves is consistent with the production of RSD/CRPS symptom profiles.

**Multiple Sclerosis**

Multiple sclerosis (MS) is an inflammatory disease in which the fatty myelin sheath insulation around the axons of brain and spinal cord neurons are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms (Compton & Coles, 2008). Multiple sclerosis affects the ability of nerve cells in the brain and spinal cord to communicate with each other effectively. Recall that nerve cells communicate by sending action potentials down long fibers called axons, which are contained within an insulating substance called myelin. Multiple sclerosis can produce almost any neurological symptom or sign, including the following: changes in sensation such as loss of sensitivity or tingling, pricking or numbness, muscle weakness, muscle spasms, difficulty in moving, difficulties with coordination and balance (ataxia), problems in speech or swallowing, visual problems, fatigue, acute or chronic pain, and bladder and bowel difficulties. Cognitive impairment of varying degrees and emotional symptoms of depression or unstable mood are also common.

In MS, the body’s own immune system appears to attack and damage the myelin (Compton & Coles, 2002). When myelin is lost, the axons can no longer effectively conduct signals. The name *multiple sclerosis* refers to scars (also known as plaques or lesions), particularly in the white matter of the brain and spinal cord, which is mainly composed of myelin. In MS, the inflammatory process appears to be caused by T lymphocytes. Evidence from animal models also point to a role of B cells in addition to T cells in the development of the disease (Iglesias, Bauer, Litzenberger, Schubart, & Linnington, 2001). Consequently, T cells appear to react to myelin as foreign (nonself) and attack it as if it were an invading virus. This triggers inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the blood–brain barrier, which in turn cause a number of other damaging effects such as swelling, activation of macrophages, and more activation of cytokines and other destructive immune proteins.

**Chronic Fatigue Syndrome**

Chronic fatigue syndrome is the most common name used to designate a significantly debilitating medical disorder or group of disorders generally defined by persistent fatigue accompanied by other specific symptoms for a minimum of 6 months, not due to ongoing exertion, not substantially relieved by rest, and not caused by other medical conditions (Sanders & Korf, 2008). Symptoms of CFS include postexertional malaise, unrestful sleep, widespread muscle and joint pain, sore throat, headaches of a type not previously experienced, cognitive difficulties, and chronic, often severe, mental and physical exhaustion.

Antibodies, such as antinuclear autoantibodies, commonly found in other autoimmune diseases have been found in patients with CFS (see Ortega-Hernandez & Shoenfeld, 2009, for review). In addition, IgM, IgG, IgA antibodies have also been found in persons with CFS (Hokama et al., 2009).

As enhanced immune function appears to be the underlying mechanism, it is suspected that CFS may be a generalized or comorbid response to one of the immune disorders noted previously. Hence, many patients with CFS appear to have other medical problems or related diagnoses. Comorbid fibromyalgia is common, where only patients with fibromyalgia show abnormal pain responses (Bradley, McKendree-Smith, & Alarcon, 2000). Fibromyalgia occurs in a large percentage of patients with CFS between onset and the second year, and some researchers suggest fibromyalgia and CFS are related. As mentioned, many persons with CFS also experience symptoms of inflammatory bowel disease or Crohn’s disease, temporomandibular joint pain, headache including migraines, and other forms of myalgia (muscle pain).

**Patterns and Conclusions**

We have considerable evidence for decreased adrenal activity, manifested by decreased cortisol output in patients with a myriad of bodily diseases. These ailments have been related to traumatic experience, and there seems to be considerable symptom overlap among them, suggesting a spectrum of related disorders with similar neuroendocrine profiles. In instances of these illness
where PTSD is not present, one may suspect, given the data noted above, that these situations may suggest hypocortisolemia resulting from glucocorticoid (cortisol) programming in utero, wherein the mothers of these patients had PTSD during the period of gestation, thereby passing on their neuroendocrine profile to their babies. Nonetheless, more studies are needed to further verify this particular phenomenon.

The data from these diseases also corroborate Rachel Yehuda’s explanation regarding the apparent discrepancies in PTSD cortisol studies, wherein she argues that methodological inconsistencies and flaws are the basis of the mixed results. Hence, the consistent evidence of hyperimmunity in each of these disorders is fully consistent with an underlying hypocortisolemic neuroendocrine profile.

The data from the cortisol and MUS studies also underscore the apparent difference between somatoform symptoms of trauma (i.e., aspects of procedural memory that are expressed, or dissociated, in somatic form) and true medical diseases that may have trauma as a putative causative effect. As we noted above, it is crucial that we understand and are able to differentiate somatic or somatoform symptoms from these immunoinflammatory illnesses. Understanding these differences has its greatest import with respect to treatment implications. Somatic symptoms, often conceptualized as manifestations of trauma in the body, are often effectively targeted and treated with EMDR as part of a comprehensive and phased trauma treatment. However, patients presenting with psychological difficulties (whether or not trauma related) and MUS must also be referred for treatment to endocrinologists, oncologists, or immunologists, in order to attempt reregulating the hyperimmune function in these patients, which is, apparently, causative with respect to their illnesses. We revisit this in detail in the following chapter, wherein we explore the implication of these neurobiological foundations on eye movement desensitization and reprocessing treatment.

**CHAPTER 9**

**Linking Consciousness, Neural Development, and Treatment**

**NEURAL DEVELOPMENT, CONSCIOUSNESS, AND EMDR**

Finally, we've arrived at EMDR, as we explore the implications of the above-mentioned issues on the adaptive information processing (AIP) model and the treatment principles that emerge from it. With reflection on the foregoing material, a number of questions come to mind. How can an appreciation of the above-mentioned data and ideas help us to understand exactly how the brain and mind change during psychotherapy? How do we utilize this knowledge regarding the neurobiology of consciousness and human development to enhance our therapeutic techniques? Can this neurobiological knowledge be utilized as a central core of understanding, rather than the myriad psychological theories of psychotherapy that often are more divisive than unifying?

The answer to these questions is, thankfully, yes. As we shall see, understanding the neurobiology of the self and of human maturation and development will make clearer many of the questions that have vexed and divided our field. Is the unconscious/implicit mind important? Should the emphasis on verbal and symbolic, left-hemispheric processing that dominates our field continue? Is the relational field or vortex that surrounds therapists and patients important? Are transference and countertransference phenomena important or just artifacts of an old theory?

Exactly how the brain and mind change during psychotherapy is the fundamental mystery that the synthesis of neuroscience and psychotherapy seeks to understand. Daniel Siegel (1999) notes that, for the most part, as clinicians, we immerse ourselves in the stories and struggles of people who come to us for help in developing beyond old, maladaptive patterns of thought, behavior, emotion, and relating. As we have already seen, both the adaptive and maladaptive patterns that our patients bring to therapy were developed in the context of relational interactions with other selves and their nervous systems.