

FUNCTIONAL SOMATIC SYNDROMES, STRESS PATHOLOGIES, AND EPIGENETICS

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Recently Henningsen, Zipfel, and Herzog described the nature and management of functional somatic syndromes (FSS).¹ They pointed out that functional somatic syndromes are “characterized by patterns of persistent bodily complaints for which adequate examination does not reveal sufficiently explanatory structural or other specified pathology,”^{1(p946)} but they are common worldwide and are seen by practically all subspecialties of medicine. They pointed out that the more common FSS described by multiple papers in the literature include the following:

- irritable bowel syndrome,
- chronic fatigue syndrome,
- fibromyalgia syndrome,
- premenstrual syndrome,
- non-ulcer dyspepsia,
- chronic pelvic pain,
- hypoglycemia,
- low back pain,
- sick building syndrome,
- Gulf War syndrome,
- tension headache,
- temporomandibular joint disorder,
- repetitive strain injury,
- multiple chemical sensitivity,
- interstitial cystitis,
- chronic Lyme disease, and
- food hypersensitivity.

Their explanation for the etiology of these diverse FSS was related to the interaction of organic disease processes, dysfunctional peripheral stimuli, and dysfunctional early and current relationships that result in the expression of “bodily stress” and associated changes in mood, including anxiety and depression. The clinical endpoint for this complex etiology is varied clinical presentations of the “loss of functioning” of the individual. The treatment approach that Henningsen, Zipfel, and Herzog suggest as the optimal program with which to manage FSS is to (1) implement a patient-centered approach to care by evaluating the

antecedents and stimuli that create the current signs and symptoms; (2) evaluate biomarkers that establish early recognition of potential dysfunctional physiology and function at the physical, emotional, and cognitive levels; and (3) focus on the context of the FSS by looking at the patient’s environment, healthcare system, and cultural beliefs. Their definition of FSS and their assessment and management follows the clinical approach described in the *Textbook of Functional Medicine*.²

One of the more intriguing suggestions derived from the work of Henningsen, Zipfel, and Herzog is the apparent overlap of FSS with the early clinical signs of chronic stress syndromes and excessive allostatic load as described by McEwen.³ McEwen points out that allostasis is the ability to achieve stable function in response to change, while allostatic load represents the integrated external and internal stress that places demands on the complex physiological neuro-endocrine-immune process that is designed to maintain allostasis. As the allostatic load increases to the point where the demands of the integrated stressors exceed the ability to maintain allostasis, alteration in the functional state of the individual appears and presents symptomatically as FSS. The understanding of this process is outside the traditional model of disease as a single entity and can only be understood at the mechanistic level by applying concepts of systems biology.⁴

The connection of functional somatic syndromes to stress syndromes then begs the clinical question: what is stress? Hans Selye in 1926 defined stress as a “non-specific response of the body to any demand placed upon it.”^{5(p53)} Since then, however, the definition has been altered to describe specific responses the body has to demands placed upon it. These responses are mediated through the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis.⁶ It is well recognized that psychological factors can be perceived as physiological stressors of both the HPA and SAM axes.⁷

What is also important, however, is the more recent understanding that many other factors such as endotoxins, xenobiotics, radiation exposure, specific food and environmental allergens, overexertion, structural imbalances, imbalanced diets, and the presence or absence of specific nutrients contribute to the integrated allostatic load and thereby contribute to the etiology of FSS.⁸⁻¹⁰

For instance, recent animal studies have found that chronic infection of the gastrointestinal tract with opportunistic organisms associated with dysbiosis results in viscerosensory signals being released through a vagal-mediated pathway from the gut to

the brain, enhancing anxiety.¹¹ It also has been demonstrated that when yeast cells are grown in an environment where specific nutrients are limited, they have altered gene expression patterns indicative of a stress response; vice versa, when the yeast cell is exposed to other environmental stressors, its nutrient needs change in response to the stress.¹²

This discovery leads to the question of how environmental or psychosocial factors could influence genomic expression and contribute to the altered phenotypes that are associated with functional somatic syndromes and later-stage stress-modulated diseases. The work of Meaney, Szyf, and Seckl at the Program for the Study of Genes, Environment and Health at McGill University in Montreal certainly helps us to understand mechanistically how this might occur. They have found that varied environmental factors epigenetically influence the materno-fetal interaction and have potential influence on the stress response throughout the life of the offspring.¹³ Epigenetic literally means “above genetics” and refers to influences on the genome that are unrelated to the genetic sequence of DNA. The genes are composed of DNA that is tightly coiled and packed within what is termed the nucleosome by binding to histone proteins in a highly structured manner. The histone proteins “shield” the DNA from damage and from being fully “read.” It is as if the book of life has sections that cannot be read because of paper clips separating certain stories (eg, genes). The paper clips represent epigenetic modification of the genome through selective processes such as methylation and acetylation. This selective control of epigenetic structure allows for only a portion of the book of life to be read in any cell and accounts for why all cells have genetic information but only a specific cell type will be able to read the information encoded in the genes specific to its personality. The “tags” epigenetically placed on the genome can be put on and taken off in many genomic locations very rapidly in response to environmental changes. They therefore seem to represent an important mechanism for how changes in the phenotype of the individual can occur rapidly in response to a changing environment without necessitating a genetic change.

Edwards et al have found in animal studies that maternal stress during pregnancy places epigenetic “tags” on the genome of the fetus, which not only alter the stress response of the offspring after birth but also turn off and on genes that are related to disease risk later in life.¹⁴ These discoveries raise many provocative questions concerning the influence of total allostatic load during pregnancy on the susceptibility of the offspring to functional somatic syndromes and other more serious stress-related diseases later in life. It also might explain the increased frequency of specific functional somatic syndromes in industrialized societies. In the past, the term “functional syndromes” was used pejoratively to describe psychosomatic illness—as if it didn’t exist except in the mind of the patient. As Wessely, Nimnuan, and Sharpe pointed out in their article “Functional Somatic Syndrome: One or Many?,” there is a substantial overlap among individual functional somatic syndromes, and the similarities among them outweigh their differences, suggesting that they share a common etiology.¹⁵ I suggest that the common etiology of these FSS is the influence of

stressors on the integrated allostatic load and the subsequent influence it has on the phenotype of the individual through altered cellular physiology modulated both through direct influence on HPA and SAM systems and through epigenetic modulation of gene expression. The unique component of the epigenetic factor is that it imparts “memory” to physiology and therefore might help explain both post-traumatic stress syndrome and the changing frequencies of FSS in offspring due to transmission of gene expression patterns resulting from maternal and paternal stress before conception and during pregnancy.

This raises many additional questions, one of which is, “What is the optimal intake of nutrients during times of increased allostatic load?” This is a complex question to answer as one would need to know the type of stressors that are influencing allostatic load, how they are perceived by the signal transduction systems of the specific individual, and what the confounding factors are that influence the regulation of specific nutrient use in the individual. These questions seem overwhelming to the point that they might never be answered. There are, however, a series of papers from Michael Fenech’s CSIRO laboratory in Adelaide, Australia, that at least open the door to a method for evaluation of this question. In 2001 Fenech authored a paper entitled “Recommended Dietary Allowances (RDAs) for Genomic Stability,” in which he discussed the fact that chemical and radiation stress factors can induce DNA strand breaks, which increase the risk to altered cellular function and disease and that increased levels of specific nutrients prevent these DNA changes under the conditions of stress.¹⁶ He has proposed that a functional RDA would evaluate the levels of various nutrients that would be needed to prevent DNA strand breaks in individuals under stress. This can be measured fairly easily by taking buccal cells from people and evaluating the impact of nutrient augmentation on their DNA strand breaks.¹⁷ He has suggested that this procedure could result in a nutrient needs assessment for individuals that would be reflective of their specific nutrigenomic and nutri-epigenomic needs.¹⁸ This is just one concept that takes us beyond the definition of adequacy to the potential of understanding how specific nutrients might provide support for maintaining allostatic reserve, thereby buffering against changes in physiology that result in FSS.

What is emerging from the field of FSS, stress, and epigenetics is the recognition that these conditions represent distortions in physiology associated with compromised allostatic load and manifest as complex symptom presentations that cut across all subspecialties of medicine. Because FSS represent a different type of illness than medicine has traditionally focused on, they require a different clinical approach, as described in the *Textbook of Functional Medicine*, for their recognition and management than a traditional disease diagnosis and also a different reimbursement system than the traditional Diagnosis-Related Groups/Current Procedural Terminology (DRG/CPT) coding procedures for their management.

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