
Book Review

Explaining “Unexplained Illnesses”

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Explaining “Unexplained Illnesses” is significant in its attempt to translate the basic science of what is known of the pathophysiological mechanisms of inflammatory biochemistry, including stress and apoptosis, for the clinical diagnostic entities of chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia, posttraumatic stress disorder, Gulf War syndrome, and others, including tinnitus. In a carefully structured format, the author presents extensive references for the hypothesis of a unifying theory for diagnosis and treatment of these diagnostic entities.

The theory proposed to “unify” these clinical entities is the nitric oxide and peroxynitrite (NO/ONOO⁻, or “no, oh, no!”) cycle. Increase in NO and ONOO⁻ and of “superoxide, intracellular calcium, transcription factor NF-κB, inflammatory cytokines, oxidative stress, vanilloid receptor activity, and N-methyl-D-aspartate (NMDA) receptor activity,” in addition to mitochondrial dysfunction, “provides a cascade of changes and stimulation resulting in positive feedback loops maintaining the cycle of activity with a clinical symptomatology reflective of pathophysiologic alteration in underlying tissue.”

Significant in our experience in support of this theory is the influence of the NO/ONOO⁻ cycle on cytosolic calcium and the demonstration of neuroprotective action by cytosolic calcium reduction of the calpain antagonist, leupeptin, reported in neurodegeneration, muscular dystrophy, epilepsy, and hearing loss secondary to acoustic trauma. In addition, for tinnitus, the reported anecdotal tinnitus relief is associated by some tinnitus patients with antioxidant therapy. Pathophysiological biochemical evidence is accumulating not only of the significance of the NO/ONOO⁻ cycle for stress but of

the increase in accumulation of excitatory amino acids and its influence on apoptosis. Clinically, stress is a known factor that results in increased existing tinnitus intensity or as a “trigger” for activation of a subclinical tinnitus (or both).

When evaluating a unifying theory for different diagnostic entities, the response to treatment is to be considered significant. Thirty-two agents or classes of compounds are listed in this work. Significantly, in our clinical experience for tinnitus (in excess of 10,000 patients since 1979), reports of tinnitus relief with selenium, flavonoids, B vitamins including vitamin B₁₂, glutathione–glutathione precursors, magnesium, NMDA antagonists, and hyperbaric oxygenation have been typified by occasional occurrence and are limited. This clinical experience does not invalidate the significance of this unifying theory for tinnitus treatment. Rather, it is considered to reflect the complexity and significance of the underlying pathophysiological mechanisms involved in tinnitus, highlighted by inflammation and stress, and the need for professionals, basic scientists, and clinicians to include consideration of the NO/ONOO⁻ cycle as a significant factor influencing the clinical course and basic treatment of chronic illnesses (e.g., tinnitus).

This text provides an excellent understanding of a complex biochemical cycle (i.e., NO/ONOO⁻). The references are excellent and provide additional resources for information, both of a clinical and a basic science nature. The author has succeeded in informing both professionals and patients of the significance of the NO/ONOO⁻ cycle for chronic illnesses, highlighted by multisensory complaints. Furthermore, *Explaining “Unexplained Illnesses”* is recommended to basic scientists, clinicians, and patients who wish to gain an understanding of and further information about the investigation, diagnosis, and treatment of chronic illnesses.

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