The American Institute *of* Stress

COMBAT STRESS

Harnessing Post-Traumatic Stress for Service Members, Veterans, and First Responders

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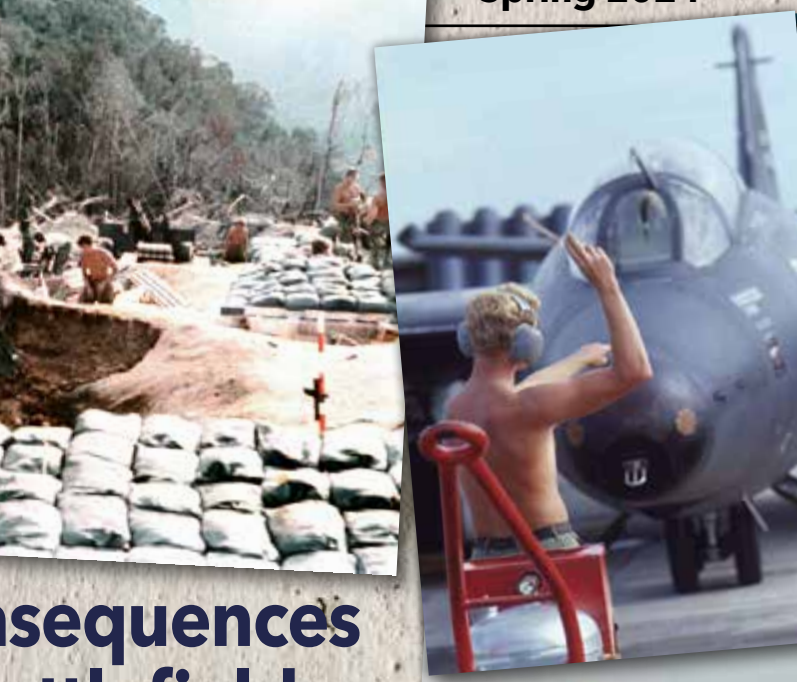
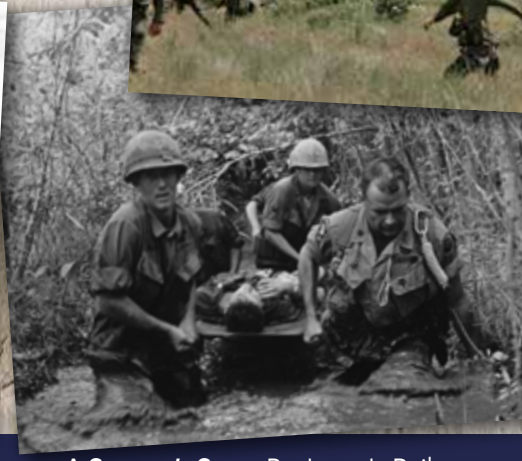


The Consequences of the Battlefield – Here, There, and Everywhere.



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Targeting PTSD's Inflammatory Biomarkers: Resolving Inflammation with Nutrition-Based Nitric Oxide Supplementation

By Stanford A. Graham, JD and Judy Mikovits, PhD

Introduction

Neurological dysfunctions are a profound health burden among Veterans, disrupting and debilitating their lives.[1] These dysfunctions are often caused by trauma. Consistent with the variety of ways trauma is experienced, neurological dysfunctions are also a varied complex of biological system dysregulation.[2] Unfortunately, even the U.S. Department of Veteran Affairs (VA) describes these neurological conditions within the unhelpful category of "mental health problem[s]."[3]

Fortunately, decades of research are slowly pealing back the layers of these disruptive dysfunctions and their causal complexities. We are learning that neurological dysfunctions are intimately connected with other malfunctioning body systems in a variety of ways. Moreover, recent science is also showing that, at a cellular level, these multi-system dysfunctions also share similar neurological pathways. For example, PTSD is experienced via pathways that are common to substance abuse, diabetes, arthritis, and Alzheimer's disease.[4] Would it surprise you to learn that PTSD symptoms regularly occur contemporaneously with chronic inflammatory symptom conditions such as obesity, type 2 diabetes, insulin resistance, chronic pain, sexual dysfunction, and cardiovascular disease?[4-7] A 2020 study published in Translational Psychiatry emphasized our more complete understanding of neurological dysfunctions this way: "PTSD is no longer classified among anxiety disorders; it is considered a trauma or stressor-related disorder... Because of the marked impact of stressors on the immune system, *it is not surprising that PTSD is associated with the immune state. Increased concentrations of pro-inflammatory factors were observed both within systemic circulation and in the brain in the context of PTSD... highlighting a close link between inflammation, stress, and PTSD.*"[6] In fact, the more inflammation we experience, the more severe PTSD symptoms become.[7]

In short, neurological disorders are causally intertwined with immune system dysregulation and its consequent impact on many other biological systems,[6] including the cardiovascular and nervous systems, the digestive, circulatory,[8] and the hepatic and endocrine systems, to name a few.[4] These multi-system malfunctions induce recurring cell-level dysregulation as well, including redox stress, disruption of telomere homeostasis, mitochondrial activity, vitamin D activation, and endothelial nitric oxide (NO) production.[9,10] These factors cause us to age more quickly, to lose our ability to metabolize our food, negatively affect our ability to think and sleep, and decrease our ability to recover from injury and illness. All these issues weaken the brain and body, making us more susceptible to illness and infection.[10]

What are these "pro-inflammatory factors" that link chronic inflammation, stress, and PTSD? They are molecules produced by a dysregulated immune system. They inflame the body, its organs, blood, and tissues, including precise brain regions. They commonly proliferate in groups, including this particular set in PTSD cases: interleukin-1 (IL-1β), interleukin-6 (IL-6),[1] tumor necrosis factor (TNF-α), interferon (INF-□), and C-reactive protein (CRP).[7] This same cytokine group is not only at the heart of PTSD, but at the foundation of XMRV, COVID 19, and Acquired Immune Deficiency/Dysfunction. Indeed, these cytokines are the biological origins of both body

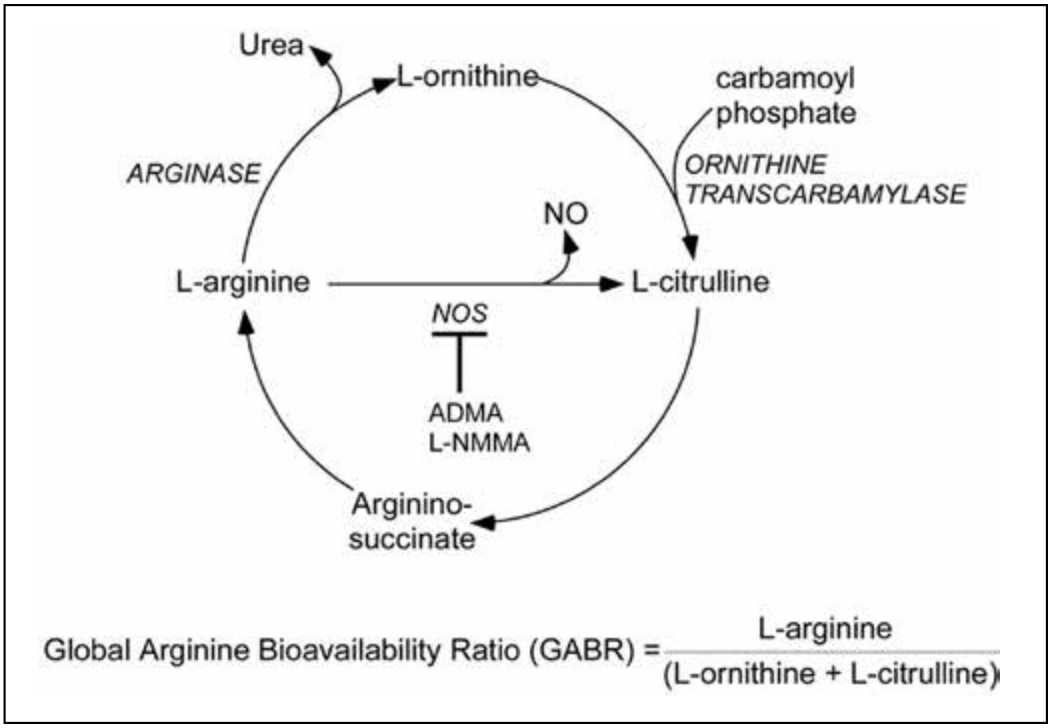

Figure 1. Schematic Illustration of Pathways for NO Production and Arginine Catabolism. ADMA = asymmetric dimethylarginine; L-NMMA = NG-mono-methyl-l-arginine; NO = nitric oxide; NOS = nitric oxide synthases.[27].

and brain disease and dysregulation.[5]

So, the question becomes how can the chronic production of these dangerous cytokines be naturally decreased while simultaneously fortifying and increasing human health? The available data suggest that targeting chronic inflammation "may serve as a potential therapeutic target for treating neuroimmune disease."[4] The good news is that there is both hope and progress. Recent research is exploring ingredient-complex nutraceuticals that act systemically throughout the human body to target these bad-acting molecules while supporting cell health.[9]

Comprehensive research analysis reveals that a deficiency of the amino acid L-arginine ("arginine") is a primary contributor to chronic inflammation and neuroimmune diseases.[11] So, now you likely have a few questions: What is arginine and how can you safely get what your body needs? What functions does arginine help your body perform to reduce inflammation? What is the relationship between arginine and NO production, and how does NO support vibrant health?[10]

What is Arginine?

Arginine is a non-essential amino acid, meaning under optimal conditions, the body can produce its own supply. It is derived from body protein breakdown or endogenous de novo arginine production in the kidneys.[11] When cells are healthy, they also synthesize arginine from the amino acid L-citrulline ("citrulline").[10] However, when cells are under catabolic stress or trauma, the body's arginine requirements dramatically increase to help address and resolve injuries and improve biological and neurological functions. Therefore, during injury and healing periods, arginine must be obtained from food intake, making arginine "conditionally" essential.[11] Arginine is abundant in seeds, nuts, meats, seafood, and soy protein isolate. Yet, despite arginine's seemingly high availability in non-genetically modified foods, the fluctuating rate at which the human body uses arginine influences its bioavailability and likely deficiency.[12,13] For example, the small intestines and kidneys collaborate in the whole-body synthesis of arginine.[14] Consequently, when these organs are dysregulated or injured, arginine deficiency is inevitable. This emphasizes the general need for nutrition-based arginine supplementation.[15]

Arginine's Function and Purpose

Arginine plays a vigorous and versatile role in the human body. It is necessary for cell division, immune system function, ammonia disposal, reparative response to trauma, and

wound healing.[16] It also supports hormone biosynthesis, including stimulating the release of insulin, growth hormone, and endogenous production of vitamin D3.[9] Arginine is also necessary for T-cell maturation and activation. One of arginine's most important functions is nitric oxide production. Arginine is the *sole fuel* specialized cells use to make nitric oxide, often referred to as the "miracle molecule." Those specialized cells are called endothelial cells. They compose the interior lining of the entire vascular system.[17] NO is a primary signaling molecule that facilitates hundreds of cellular, organ, and biological system functions. This is why arginine deficiencies inevitably result in NO deficiencies. In turn, NO deficiencies invariably lead to immune system dysfunction, blood dysregulation, and the spiraling proliferation of dangerous cytokines and inflammatory diseases, including PTSD.

PTSD and Global Arginine Bioavailability Ratio

Recent research shows that solving arginine deficiency and inadequate NO production helps resolve PTSD symptoms and associated inflammation-caused comorbidities.[10] In 2016, an international research team was the first to measure arginine levels in Veterans with PTSD who had inflammatory levels of IL-1β, Il-6, TNFα and IFNμ.[10] Their purpose was to explore the causes of, and possible new therapeutics for, neurological and biological aspects of PTSD.[7] The team discovered a surprising and direct connection: The inflammatory molecules proliferated when the Veterans had low blood serum levels of arginine. With this observation, the team's understanding of PTSD expanded "from a purely mental illness to an illness with important somatic manifestations" which could "lead to novel treatment options for both the psychiatric and somatic aspects of the condition."[7]

The research team called their diagnostic tool the "global arginine bioavailability ratio" (GABR). This ratio identifies the amount of bioavailable arginine in blood serum compared to the combined amounts of two other amino acids, ornithine and citrulline. The research team found that higher levels of bioavailable arginine, with consequent higher levels of bioavailable NO, predictably resulted in lowered PTSD symptom severity. They emphatically concluded: "The present study provides the first evidence that the global arginine bioavailability [ratio], a marker of NO synthetic capacity in vivo, is decreased in Veterans with PTSD and is negatively associated with markers of inflammation as well as with measures of PTSD symptom severity."[7] In short, Veterans with PTSD symptoms were experiencing arginine and NO deficiencies. Thus, increasing both arginine and NO bioavailability decreased inflammatory bio-marker levels and PTSD symptom severity.

Nitric Oxide and its Functions

As previously stated, endothelial cells are the engine of endothelial NO production. NO creates both good outcomes and prevents bad ones. First, adequate supplies of NO regulate and optimize blood flow, blood viscosity, blood speed, blood oxygenation, vessel flexibility, insulin production, cell cleansing (autophagy), and much more. Additionally, NO maintains the cleanliness of blood vessels, blocking adhesion of blood platelets, lipids, bacteria, and other matter to the inner vascular wall. Hence, NO helps prevent strokes, unwanted blood clotting, hypoxia, and

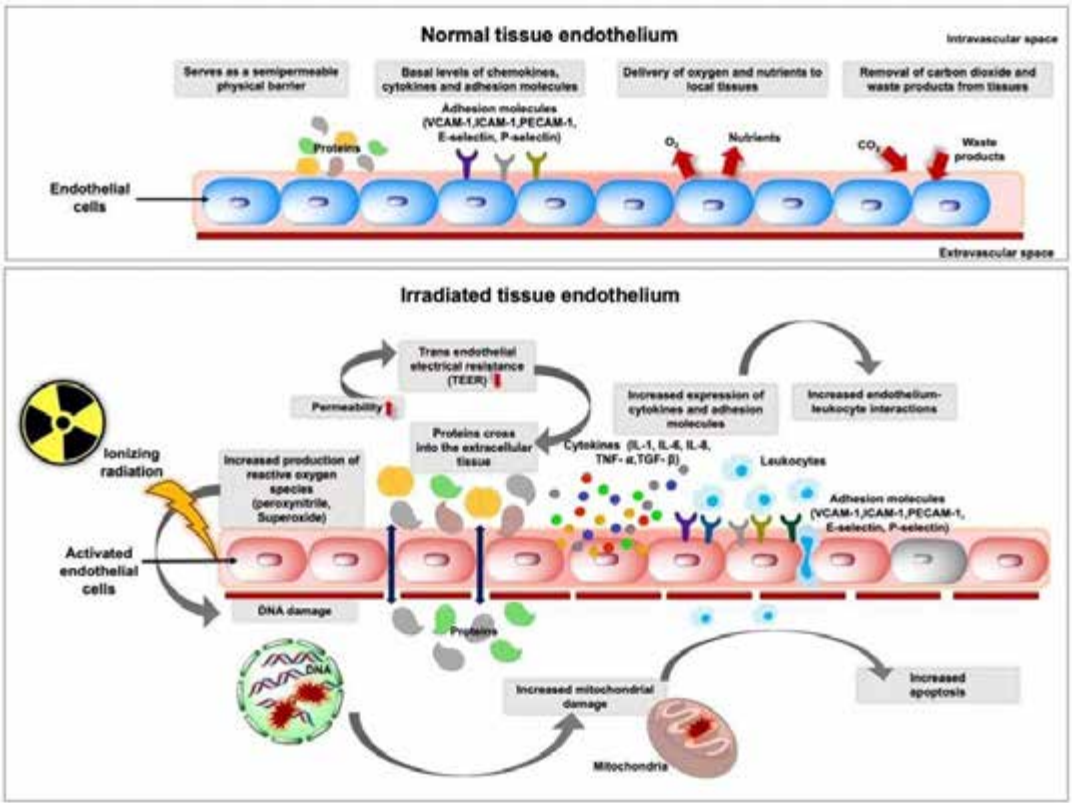

Figure 2. Overview of vascular endothelium and mechanisms by which IR impacts endothelial cell regulation. Top panel: Normal tissue - Endothelial cells act as a semipermeable barrier that regulates the delivery of nutrients and oxygen to tissue and the removal of carbon dioxide and waste products. Normal endothelial cells have basal levels of some adhesion molecules. Bottom panel: Irradiated tissue – Ionizing radiation increases the production of ROS leading to DNA and mitochondrial damage and increased apoptosis. IR also alters endothelial permeability by acting on tight and adherens junctions allowing excess extravasation of proteins to cross into the extracellular tissue. Radiation exposure also increases the release of proinflammatory cytokines and chemokines and upregulation of adhesion molecules resulting in increased leukocyte-Endothelial cell interaction and trafficking to vital organs.[28]

inflammation.[10] NO deficiency, on the other hand, leads to strokes, atherosclerosis, and the proliferation of oxidative reactive oxygen species ("ROS") throughout the body. In fact, NO deficiency is also the common denominator of many chronic inflammatory diseases, including hypertension, diabetes, aging, heart attack, Alzheimer's disease, Parkinson's disease, epilepsy, migraine, and other neurodegenerative diseases.[10] Maintaining healthy NO production is, therefore, key to sustained functional health. So, how do we prevent NO deficiency?

Mechanisms of Arginine and Nitric Oxide Deficiency

Arginine deficiency is created in two major ways. First, it results from an unhealthy diet. Second, stress, trauma, and inflammation cause the over-production of arginase, an enzyme that ravenously consumes arginine, resulting in too much ornithine.[18] "Overly active arginase can reduce the supply of arginine needed for the production of NO, leading to an over-supply of ornithine. Too much L-ornithine can lead to structural problems in the vasculature, neuronal toxicity, and abnormal growth of tumor cells."[18] An increase in ROS and inflammatory molecules promote pathological elevations of arginase activity.

Arginine metabolism by arginase, which lowers NO production in PTSD sufferers, is a function of commonly experienced and repeated fact patterns in the lives of Veterans:

- Physical trauma, including battle wounds involving bullets, bombs, shrapnel, burns, broken bones, tissue damage, critical illness including bacteria, viruses, infection, and prolific pro-inflammatory concentrations;[11]
- Psychological trauma, including seeing and hearing death, social destruction, profound injuries to humans, observing, and participating in intense human suffering;[11] and
- Invasive medical treatment and recovery, including blood transfusions and ion radiation.[17]

For example, wounds, whether physical or mental, require higher amino acid levels to heal.[11,17] Typically, all Veterans have inadequate levels of global arginine during wound and healing periods.[11] Thus, their NO levels are also reduced, prolonging the healing process.

Next, infection is a tremendous biological and neurological stressor via the immune system. Approximately 10% of all trauma patients develop wound infections. Infection rates soar to 30% in those who remain in the ICU for over 48 hours. Tragically, infections are the leading cause of late organ failure and contribute up to 10% of all trauma-related deaths.[11] Infection also reduces already low levels of arginine thereby decreasing NO production and compromising the healing process.

Additionally, blood transfusions cause arginine and NO deficiencies. A 2011 study found that blood transfusions impair NO production and cause endothelial dysfunction." Moreover, stored red blood cells ("RBC") cause the accumulation of free hemoglobin that consumes NO at a rate 1,000 times faster than when it is bound within healthy RBC. Hemolytic RBC's also releases arginase, causing substantial reductions in intravascular arginine.[19] The result? Drastically decreased arginine, decreased NO and increased vascular damage.[13]

Next, ionizing radiation in the form of CT scans, PET scans, and x-rays immediately injures endothelial cells. This compromises NO production while simultaneously causing the proliferation of IL-1, IL-6, TNF-α and TGF-B, the very causes of PTSD symptoms.[20]

The final mechanism of NO deficiency is a molecule called superoxide. When the body makes NO it inevitably creates superoxide. When NO and superoxide combine, they form a new molecule called peroxynitrite, considered "one of the most destructive molecules in the biological milieu."[10] Hence, helping the body create healthy NO while simultaneously reducing peroxynitrite formation is imperative for healing, sustained health, and vitality.

This brief list demonstrates the catastrophic health consequences that can occur during common medical procedures, in addition to the those caused by the trauma being treated. These fact patterns emphasize the need for supplementing arginine in a healthy and thoughtful way, with proven nutrition-based supplements. These scientifically proven products can safely increase bioavailable arginine and long-term NO production while reducing peroxynitrite production. Perhaps most importantly, proper arginine supplementation can help Veterans reduce the inflammatory agents that manifest in PTSD symptoms.

Erectile Dysfunction

One final disorder associated with PTSD that warrants our attention is erectile dysfunction (ED). Research shows that ED is an expression of relational, psychological, and biological components.[21] It is associated with aging and PTSD systemic comorbidities like cardiovascular disease (CVD), hypertension, diabetes, and depression. Smoking, alcoholism and drug abuse are related behaviors. If you suffer with ED, you are not alone. It afflicts 25% of men younger than 59 and 61% of men over 70.[22]

Research also reveals that "NO is the primary biochemical mediating erectile function." Thus, we know that endothelial dysfunction, low NO production and minimal NO release are the chief

mechanisms of organic ED.[22-24] So what can you do? Supplement wisely with an arginine-based nitric oxide supplement. Studies show that arginine-derived NO is a vasodilator that controls systemic and penile blood flow and plays a singular role in erectile function.[25] Studies have shown that arginine-induced NO boosts desire and sexual arousal, thereby increasing libido. It also relaxes "the smooth muscles in the genital area, allowing for increased blood flow and heightened sexual pleasure."[26] Supplementing with NO can improve your relationships, health, and mental well-being.

New Therapeutic Models and Solutions - Cardio Miracle

The need for nutrition-based solutions that target inflammatory molecules is clear.[7] Fortunately, recent studies not only support these conclusions, but also demonstrate their existence and application. When testing a NO supplement product called Cardio Miracle (CM) in their nanotechnology lab at Ohio University, researchers found that 6 grams of its amino acid complex, including arginine, when consumed together with specific mixtures of over 40 anti-inflammatory and antioxidant foods, not only induced long-term production of bioavailable NO, but also significantly downregulated peroxynitrite production.[10]

In 2022, ground-breaking research focused on the same NO supplement, CM. That study showed that long-term production of NO activated vitamin D3 production in the body. This biological process was previously unknown. In addition, the study revealed that CM's specific formula down-regulated the specific group of pro-inflammatory cytokines associated with PTSD symptoms.[9] This research directly supports the conclusions reached in the GABR research: Targeting inflammation with nutrition-based products can resolve underlying inflammatory causes and reduce the biological consequences and symptoms associated with PTSD and other neurological dysfunctions.

In conclusion, Cardio Miracle helps maintain healthy, systemic arginine levels, supports long-term endothelial nitrous oxide production, and down-regulates peroxynitrite and the specific group of pro-inflammatory cytokines associated with PTSD symptom severity. Accordingly, supplementation with Cardio Miracle should be seriously considered in ameliorating the negative neurological and biological dysfunctions associated with PTSD and associated injuries suffered by Veterans, their friends, and families.

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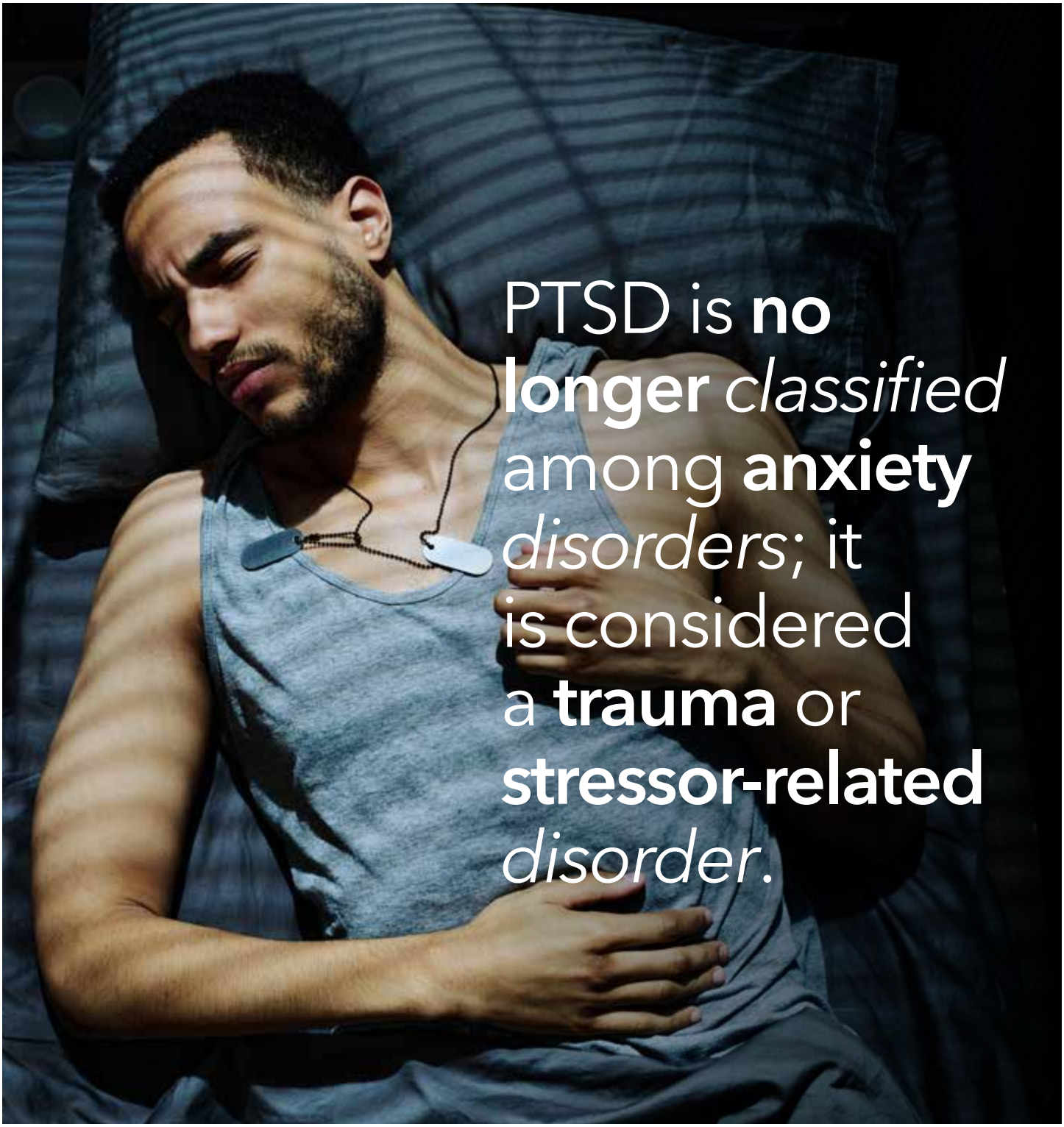

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Stanford Graham earned a BA in Philosophy from Brigham Young University in 1987 and a Juris Doctorate from Villanova University School of Law in 1992. He practiced law in the areas of corporate governance, corporate veil theory, and asset protection, culminating with specialties in international commodity transactions. He is an autodidact in many areas, including biology, hematology, and physiology. He has served Sanacor International, Inc. with distinction regarding its scientifically substantiated Nitric Oxide supplement, Cardio Miracle (www.cardiomiracle.com), brilliantly formulated by founder/CEO John B. Hewlett. Graham has developed the refulgent understanding and relevance of the product's scientific foundations and its myriad benefits to systemically integrated biological functions in humans. An elite athlete, he is a miler and short distance runner pursuing performance records in the 50+ year men's categories.

Dr. Judy Mikovits earned a BA in Chemistry from the University of Virginia in 1980 and a PhD in Biochemistry and Molecular Biology from George Washington University in 1992. In her forty-year quest to understand the causes, prevention, and treatment of chronic diseases, she has co-authored seminal papers culminating at least a decade of research in each of four fields: Immunology, natural products chemistry, epigenetics, and HIV/AIDs drug development. In 2009, Dr Judy Mikovits led the team that first isolated and characterized a new family of human disease-associated retroviruses, XMRVs. She has co-authored more than 50 peer reviewed publications and book chapters and holds a patent for Combination Therapy for Prostate Cancer using Botanical Compositions and Casodex. She is also a *New York Times* Best-selling author. Her passion is botanical drug development and personalized nutritional therapeutic solutions.