Assessing and treating the effects of Neuroinflammation as the precipitating cause for neuropsychiatric conditions leading to suicide.

An established program since 2009.

Team description

1. **Mark L. Gordon, MD**. Is a civilian physician, originally residency trained, and board certified in Family Medicine, moved into Endocrinology in 1995 and then Neuroendocrinology in 2004. A survivor of multiple TBIs, he sought an understanding of the relationship between neurotrauma, neuroinflammation and the effects on the neurochemistry influencing the brains functioning, cognition and emotional presence.
2. **Andrew Marr** is a retired Sergeant First Class Green Beret from 1st Special Forces Group. Co-author of the best-selling book, Tales from the Blast Factory and contributing member of award-winning documentary Quiet Explosions. A graduate of Texas A&M (B.S.) and Pepperdine (MBA) and current CEO of Warrior Angels Foundation.
3. **Andy Riise** is retired US Army Lieutenant Colonel who was the first Master Resiliency Trainer and worked hand in hand with University of Pennsylvania in the creation of the program to prevent soldier suicides. Has served as a mental skills coach for the Cincinnati Reds, the Colorado Rockies, and multiple Special Operations Units in the US Military.

Veteran Impact: Our program presently provides direct care to over 550 veterans throughout the United States, with another 581-awaiting enrollment. Within these groups are representatives from the Vietnam era to the present including veterans, and active-duty members, as well as those facing medical retirement. We prioritize enrollment into the program in those deemed highest risk, based upon an initial phone conversation with Dr. Gordon, a patient's self-assessment, and the level of care being provided by their VA caregiver or other providers. We have the ability to provide pre-enrollment support from veterans who have gone through the Millennium-Warrior Angels program, thereby helping to guide them through a path to healing. The advantage of this solution is we can reach veterans anywhere in America within 24 hours and provide a structured program during their recovery. If desired, we are open to partnering with a specific VISN or center and their known population, or a mixture of the two.

Foreword: Since 1997, the Millennium Health Centers, Inc under the direction of Mark L. Gordon, MD, has been working on the issue of trauma induced hormonal changes in the brain. In 2004, the focus included the impact of these hormonal deficiencies on psychological and cognitive functioning. Between 1997 and 2008, we applied our developing technology on all comers until 2009, when we had our first Green Beret who after multiple deployments and frequent firefights, suffered with depression, insomnia, irritability, and fatigue as his primary complaints. He had the biomarker panel performed which directed his treatment. His wife, an ER physician, provided his treatment which resolved his symptoms allowing him to extend his enlistment at Fort Bragg as opposed to being medically discharged (retention). Between 2009 and 2015, our Veteran's community continued to grow as knowledge of our results became public. Our military program accelerated in 2015 when Andrew Marr entered our program. At that time, this SFC, Army Green Beret was dealing with depression, paranoia, alcoholism, cognitive impairment, and suicidal

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ideation, although he was undergoing treatment on 13 medications and psychotherapy. Within a short time of starting his treatment protocol, based upon his biomarker panel results, his mood disorders stabilized, he was taken off his medication, and he was starting to return to who he once was. As he progressed, he returned to university to get an MBA from Pepperdine, co- authored a book that was made into a documentary movie - **Quiet Explosions** (highly suggest seeing it.). Andrew and his brother Adam (Army Apache pilot) founded the Warrior Angels Foundation (501c3), to provide the Millennium's protocol to other veterans in need. Since then, the Millennium Health Centers and Warrior Angels Foundation have worked together to provide our program to over 550 US military service personnel providing grants and subsidy for the program. Andrew and I were invited to a number of military bases at the request of the Commanding Officers due to the recognition of the program's success; SEAL Team 6 in Virginia Beach, Fort Carson, Fort Bragg, Camp Pendleton, and Portsmouth Naval Hospital to present our program in a Grand-Round for the medical department. In 2020, I was invited by the Ministry of Defense of the UK, to come to Imperial College to explain to the Military Surgeon General why their top SAS Majors were flying over the pond to be assessed and seen by the Millennium Health Centers. The health care providers at the College were not ready for our solution or the answers, but nonetheless, the Military Surgeon General offered our group $15 million (£12M) to develop a program at The Queens Hospital in Birmingham England. Unfortunately, Covid interrupted this project.

A Proposed Solution in Three-Parts:

(1) **Biomarkers of Trauma:** Trauma causes inflammation either above or below the neck while polytrauma, generates it ubiquitously. Regardless of origin, the inflammatory cytokines (IL-1, IL-1B, IL-6, and TNF-alpha) pass into the brain disrupting the blood brain barrier as well as altering the healthy neurochemistry of the brain. Markers of the effects of this process are found within the neurosteroid and neuroactive steroid pools of hormones. Therefore, in order to provide objective treatment, looking at the patterns of neurosteroids produced by the brain and the neuroactive steroids regulated by the brain's intact endocrine and neuroendocrine systems becomes the source of our primary solution: **Identifying the Problem**.

The Millennium has developed a biomarker panel which consists of 24 measured markers and 2 calculated ones (Chart 1). This system of testing has already been applied in over 550 service members and 3200 civilians since 2004. When there is trauma to the hypothalamus (blast wave trauma) it can lead to dysregulation of sensitive hormones like growth hormone (GH), Prolactin (PR) and Insulin (IN). Additionally, trauma precipitated inflammation can inhibit production of luteinizing hormone, follicle stimulating hormone, and free testosterone(male) or estradiol (female). Measuring inflammatory cytokines would be a more direct means of identifying those individuals at risk for hormonal dysregulation, but we found inconsistencies in the correlation of cytokine to neurosteroid levels. Since cytokines are produce all over the body, the identification of those that are generated strictly in the brain, is undistinguishable.

Once the biomarker panel members were identified, the question became how to interpret them individually and in relational groups. The standard of care regarding laboratory results, is based upon pre-existing reference ranges that healthcare providers use to identify deficiencies, "normalcy", and excesses of any marker. If a hormone has a range of 20-80, and a result is 21, it is read as "within the range" and therefore "normal". The fact that the individual has significant symptoms is commonly ignored. The success of our protocol has been in bringing the levels of most biomarkers to their 50^{th} – 75^{th} percentile of the stated laboratory's range. The relationship

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between certain markers can tell us about hormonal dysregulation, e.g. LH-Testosterone or Estradiol, GH-T4, TSH-T4, TSH-Prolactin, GH-Prolactin, DHEA-s-Testosterone, Cortisol-TSH, Pregnenolone-GABA and many more hormone sets all altered by neuroinflammation.

Returning the level of these hormones to optimum has been associated with improvement in emotional and cognitive functioning.

(2) **Accelerating Adaptability**: The proficient application of the science involved in endocrinology and neuroendocrinology can take years to achieve. Acknowledging the complex interactions of neurosteroids and the neuroactive steroids, provides for a challenge in the interpretation of these biomarkers for optimizing treatment. Furthermore, there is a need to include in the interpretation of these biomarkers, the influence of specific medications on their measured levels. At this point, there is a need for an AI machine learning system to deal with these complex issues. **Leveling the Playing Field**.

Throughout a health care provider's career, they develop a large compendium of medically related algorithms to help solve challenges such as that presented by Mission DayBreak. Therefore, how do we provide for a solution that can be assimilated across multiple VA facilities rapidly and with a consistent interpretation of the biomarkers and generation of treatment that follows; Primum no Nocere? The Millennium Health Centers, Inc. has developed a directed, machine learning software application, that assists the healthcare provider in the interpretation of the hormone biomarkers regardless of the laboratory performing the testing. It also integrates the effects of medication and supplements on many of our hormonal pathways which can produce an artificial increase or decrease in one or more members of the biomarker panel. As an example, the medication bupropion has a dopaminergic affect in the body which can increase growth hormone production and release, decrease T4, increase T3, elevate Prolactin causing a decrease in luteinizing hormone, thereby reducing the production of testosterone and estrogens. Without this knowledge, misinterpretations with unnecessary treatment for perceived deficiencies or excesses will be made. The use of this AI system, aside from providing diagnostic predictability and supporting treatment interventions, will augment clinical workflow, allowing for a greater number of Veterans to be seen and treated. The Millennium Office Laboratory Assistant (MOA) is scalable to your needs, with consistent and reproduceable reporting. (The MOA is a cloud-based application that is presently in 50+ clinics in 6 countries. https://MillenniumAPP.ai).

(3) **Treatment**: The Millennium's treatment protocols are based upon a combination of hormonal replenishment and select nutraceutical products identified to reduce neuroinflammation. When each biomarker is analyzed by the MOA, it is graded as to being low (deficient), normal, or elevated (excess). If deficient or excessive, the appropriate standard of care is invoked, and a treatment protocol is suggested. If the result is within the "normal" reference range, it is classified into its quartile based upon its given range. The report and treatment suggestions generated by the MOA, is based upon the goal of returning the majority of the biomarkers to their 50^{th} to 75^{th} percentile of range (e.g., IGF-1, Free Testosterone, DHEA-s, and Vitamin D3) and the others to their 25^{th} to 50^{th} percentile of range (e.g., Estradiol in males & Testosterone in females). ***The Intended Impact***

Treatment is separated into two parts: (1) replenishment of hormones and (2) reduction of neuroinflammation. Replenishing deficient or insufficient hormones to their optimal levels is enhanced by using treatment approaches that initially attempt to restart one's own production. Since 2012, the Millennium initiates treatment of hypogonadal males with Clomiphene citrate and

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not with either injectable or topical testosterone. The rationale is that exogenous testosterone has the potential of completely shutting down the recipient's natural production of testosterone which might not be restored thereby, committing them to life-long replacement. Instead, the scientific literature identified that neuroinflammation interrupts the production of hypothalamic-pituitary release of luteinizing hormone and the natural production of testosterone. Stop the inflammation and you have a chance of restarting natural production of testosterone. The use of Clomiphene with anti-inflammatory nutraceuticals has been effective in raising natural testosterone production. A similar approach has been provided for Growth Hormone since 2006, where an oral secretagogue is used to stimulate five pathways in the brain causing a more normal production of growth hormone.

As stated above, trauma creates free radicles that raise the oxidative stress level by activation of microglia. Therefore, enhancing the body's ability to neutralize the added production of free radicles would reduce the activation of microglia and their relative production of cytokines. Our Glutathione system is the front line of defense against these free radicles. In cases of trauma with the attendant increase in cortisol, this system becomes overwhelmed and dysfunctional allowing for microglial activation. The use of a nutraceutical blend of N-acetyl cysteine, ascorbic palmitate, gamma tocopherol, PQQ, and EGCG reduces neuroinflammation responsible for impeding the natural production of Serotonin, Melatonin, Epinephrine, Norepinephrine, and Dopamine. In our cases, reduction in neuro-inflammation has also been associated with improved sleep, reduction in pain, and reduction in the frequency and intensity of migraines.

Based upon the aforementioned, we would apply our solution to veterans and active service personnel who have sustained a mild to moderate neurotrauma secondary to any form of blast wave trauma and who suffer with depression, insomnia, and fatigue with or without suicide ideation. Blast wave trauma can be represented by IED, shoulder mounted armament, controlled breaching charges, artillery fire, and repetitive gun fire.

Steps to implementation of our solution would be: (1) Initiation of assessment with the Biomarker panel which is (2) interpreted by the MOA giving suggested treatment, that is (3) delivered to the veteran at their place of residence. (4) They will be monitored on a monthly basis with the MPQ and a cohort leader who has already participated in the protocol. (5) We will monitor blood work at 3mo, 6mo and annually, until (6) the patient achieves the desired goal of improvement. Throughout the process there is access to multiple modes of support within our online platform. For additional educational tools that delve into the academic science that was used to develop this program, we offer the book, ***TBI – A clinical approach to diagnosis and treatment***, a live 8-hr lecture program, and an on-line seven lecture series on the science of assessing and treating Symptomatic TBI (PTSD). We also support the integration of sleep, fitness, nutrition, and other modalities that utilize the same foundational approach to healing while still providing for individualized care.

Part 2: Evidence framework. Demonstration of **evidence-based decision-making** in developing this solution, as well as a framework for defining success, including any relevant citations needed.

Since 2009, the Millennium Health Centers, Inc. has been working with active-duty members and veterans with TBI and PTSD. Many of these individuals have had suicide ideation with actual suicide attempts while on a compendium of medications. They were enrolled, as patients, into the Millennium-TBI Protocol having their blood drawn for the biomarker panel which was processed by an independent clinical laboratory. Their laboratory results were then used to direct

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a personalized treatment protocol. Every patient received a group of nutraceutical products that specifically reduce inflammation. Hormonal supplementation was based upon a finding of a result that was less than the median of the laboratory's range. Thereafter, each patient was monitored with a monthly program questionnaire (MPQ) which asks 20 subjective questions that are graded from 0-10 (ten is the highest positive response). These questions assess the psychological, physiological, and physical functioning of the individual. The MPQ results are used to generate annual reports on patient program outcomes (www.tbihelpnow.org/the-science).

Within the scientific literature was an ample amount of research supporting a translational medicine approach for our development of both laboratory testing and treatment protocols. In the Millennium's development of the biomarker panel, we addressed the patterns of hormonal loss associated with trauma, both physical and non-physical. The biomarker panel also assesses supportive hormones that help to diminish inflammation such as DHEA, Pregnenolone, and Vitamin D3. The development of the Millennium's treatment protocol was based upon published research studies which we tested in a clinical setting using a trial-and-error methodology. If a single nutraceutical was found to have a positive effect on the patient's symptoms, a second nutraceutical was tested and then added to the protocol. An example is N-Acetyl Cysteine (NAC) and γ-Tocopherol, each showing beneficial effect on mood, sleep, and irritability. When combined they had an even higher efficacy. At the end of this procedure, we had a nutraceutical treatment package which was used in our 2020/2021 Marine project.

The Millennium started developing protocols in 2004, deriving its evidence-based decision-making process from research that had already been performed and published in peer-reviewed articles. The science provided, gave us an understanding of the relationship between the brain's production of regulatory hormones and neurotransmitters, and their deficiency status post-TBI, which allowed for the development of a diagnostic biomarker panel that looks for these pathognomonic changes attributable to trauma (1,2). Addressing these changes allowed for the development of treatment protocols focused on mitigating the adverse effects of neuroinflammation while concurrently correcting deficient neurosteroid levels (3,4).

Immediately following trauma, the level of pro-inflammatory chemistry rises (5). If the trauma is below the neck, the proinflammatory cytokines produced will pass into the brain activating microglia, which in-turn will initiate their own proinflammatory cytokine production adversely affecting the brain's neurochemistry (6). When the trauma involves the head, microvascular hemorrhages, dural and subdural hematomas, and diffuse axonal injury, can cause a rise in oxidative load with microglial activation, further raising the level of oxidative stress (OS). Glutathione is considered the first line of defense in the brain with free radical scavenging being a primary function. Due to the excessive level of OS, glutathione is consumed, diminishing this first line of defense with further elevation in free radicals (7).

The presence of elevated levels of reactive oxygen and nitrogen species, and peroxynitrite compromise many of the enzymatic pathways causing loss of neurotransmitters, neurosteroids, neuroactive steroids, and mitochondrial function (8). This is commonly seen in TBI patients who present with fatigue, depression, and insomnia (9). This triad of symptoms is the direct result of neuroinflammation that inactivates the enzymes tryptophan hydroxylase and tryptophan decarboxylase, thereby stopping the conversion of tryptophan to serotonin and then to melatonin (10,11). The Millennium has documented these symptoms in nearly 100% of our veterans.

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As neuroinflammation rises, the inflammatory cytokine IL-1-beta inhibits luteinizing hormone production, thereby reducing Testosterone and Estradiol production. (12,13) The benefits of estradiol besides enhanced neuroplasticity, is regulation of neuroinflammation (14), as testosterone has been shown to directly decrease inflammatory cytokines (IL-1, IL-1B, IL-6, and TNF-alpha) while also increasing the major anti-inflammatory cytokine, IL-10 (15).

As physical and psychological stress develops as part of the injury, so does elevated levels of cortisol which decreases thyroid stimulating hormone (TSH) and growth hormone (GH) levels, thereby raising the risk for depression and suicide (16,17). Additionally, elevated cortisol is responsible for the loss of Fractalkine, a key modulator and suppressor of microglial activation which controls neurotoxicity (18) and appears to be a mechanism for purely stress-induced Post-Traumatic Stress Disorder, as now documented in US military service members (19).

Because neuroinflammation disrupts the brain's neuropermissive environment, the hypothalamic-pituitary thyroid axis is affected. This is usually seen as a central loss of TSH and the peripheral decrease in T4 and T3 production by the thyroid gland. The Jostle index (TSH index) is a mathematical relationship between TSH and T4, such that, when the TSH-index is below 1.3, indicates that a central event has occurred to create the measured loss (20). We often see the TSH index below 1.3 in those exposed to blast wave trauma (21).

These biochemical and pathological changes in the regulation of the brain's chemistry, is for the most part, responsible for the development of debilitating neuropsychiatric conditions; specifically, depression (22). When depression is the prominent expression of the brain's toxic environment, suicide ideation and suicide are not far away. Many of our US military service members have treatment resistant depression (TRD) which is clinically associated with the inability of one or more anti-depressive medications to improve their depression (23). In the Millennium's experience, based upon results of the biomarker panel, deficiencies of Growth Hormone, (24) DHEA-s, (25) Free Testosterone, (26) Thyroid, (27) and Vitamin D (28) are all associated with this form of treatment resistant depression (29,30).

Success for us would start with changing the paradigm by which our military personnel are assessed for trauma related injuries. This would entail acknowledging that you do not need to have loss of consciousness, amnesia, or confusion after a trauma to have the onset of neurochemical disruption. Recognizing that there are physical and non-physical traumas that can elicit the same neuropsychiatric outcomes, over time, due to generation of the same toxic cytokines and radicals. Therefore, performing an assessment of neurosteroids, neuroactive steroids, and supportive hormones at the beginning of all evaluations, will provide evidence for treatment intervention. Ultimately, success will be represented as an improvement in clinical symptomatology above 50%, within 3-6 months, based upon MPQs. Ideally, there would also be a diminution in prescribed medication as well as improvement in depression, reduced suicide ideation, resolved insomnia, and a greater sense of well-being.

Implementation plan: The healthcare system would draw the biomarker panel, which is non-gender specific, using any clinical laboratory. The results are entered into the AI Program App (MOA), which interprets the labs with integration of medication, supplements, and surgical procedures, and offers predictive diagnoses and support for treatment options (31-38). The system is scalable in not being limited by the education of the healthcare provider since the AI does the heavy lifting. Additionally, being cloud-based there are no real limitations on the number of users or patients that can be entered into the application. Nonetheless, it would be ideal to have the

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system users and healthcare providers learn the science that is associated with the systems development.

Needs identification: The implementation of an AI resource is always met with opposition due to concerns about trust in the system, consistency of output, and explainability of the results. Based upon my recent training at MIT Sloan School of Management dealing with AI in Healthcare, the Millennium's AI solution has met the rigor of the requirements on all aspects of the design and interpretability and therefore, predictability. Most importantly, is that the machine learning was derived from thousands of actual patients and the resultant algorithms were used to develop the final program which has been validated by its use in multiple medical facilities.

An opportunity to demonstrate the efficacy of the program, in real-time, is all we are asking for.

Chart 1. This is the initial Millennium biomarker panel performed on each of our veterans, as well as civilians, for a comprehensive assessment of neuroactive and neurosteroid levels.

Growth Hormone	IGF-1	IGFBP-3	DHEA-s	Free Testosterone	Total Testosterone
DHT	SHBG	Estrone	Estradiol	Luteinizing Hormone	FSH
Pregnenolone	Progesterone	Prolactin	Zinc	Insulin	Vitamin D
TSH	Free T4	Free T3	rT3	ACTH	Cortisol
Calculated Markers	TSHi	T3/rT3 Ratio		Predicted Free T	

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