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Letter to the Editor: Potential Contribution of Hyperbaric Oxygen Therapy to A New Vision of Transformative Medical Research via NIH to Make America Healthy Again

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Letter to the Editor

The New Vision of Transformative Medical Research via NIH to *Make America Healthy Again* (MAHA) [1] involves four priorities: 1) Preventing, reversing, and treating iatrogenic illnesses 2) Addressing the country's mental health crisis 3) Combating diabetes and metabolic disorders and 4) Mitigating the rise of autoimmune diseases. While research is a necessity, its timeline precludes implementation of results in the narrow 2–4-year window of the New Vision. Effective treatment of the illnesses in #'s 1-4 could have a rapid impact and the only therapy that has both stand-alone and adjunctive potential to achieve this is hyperbaric therapy/hyperbaric oxygen therapy.

Hyperbaric therapy (HT)/hyperbaric oxygen therapy (HBOT) is a 362-year-old therapy [2] that has been applied to over 132 conditions [3]. It is a treatment for common acute and chronic wound pathophysiology [4-7] found in acute and chronic wound [4-9] and inflammatory conditions [4-12]. Composed of increased barometric pressure and hyperoxia [13] it takes advantage of all living organisms' sensitivity to changes in environmental pressure [14] and oxygen. When delivered intermittently HT/HBOT exploits this natural phenomenon to have wide-ranging effects on disease pathophysiology [4].

The core effect of HBOT is its epigenetic DNA signaling capability [15] that became understood in 2009 and 2010. In two experiments, HBOT demonstrated independent, overlapping, and interactive effects of increased barometric pressure and increased pressure of oxygen [16] on 8,101 of the 19,000 (40.3%) protein-coding genes embedded in our 46 human chromosomes [17]. The largest clusters of genes turned on were the anti-inflammatory genes and the growth/repair hormone genes, while the largest clusters of temporarily suppressed genes were the pro-inflammatory genes and the genes coding for programmed cell death. These two experiments explained 346 years of application to wounding and inflammatory conditions by showing inhibition of inflammation, stimulation of tissue growth/repair in damaged areas, and cessation of programmed cell death with every exposure to increased barometric pressure and increased oxygen (a hyperbaric treatment).

These two discoveries can impact the four cornerstones of the New Vision as follows:

1. **Preventing, reversing, and treating iatrogenic illnesses**: HBOT's effects on mitigating iatrogenic illnesses are partially dependent upon predicting the iatrogenic illnesses. In the case of medication errors and other unpredictable medical errors, pre-error administration of HBOT is impossible. In those cases, many of which result in "wounding" conditions characterized by the inflammatory process, an extensive literature documents the beneficial effects of HBOT on treatment of hypoxic/ischemic reperfusion injury (RI)[18-25], particularly the white blood cell mediated component [19-23] RI is the inflammatory injury pathophysiology when interrupted blood flow is re-established, but also occurs after nearly every insult to the human body that involves wounding/tissue injury due to hypoxia, ischemia, mechanical, chemical, or electric insults. First identified in the signature diagnosis of the hyperbaric medicine specialty, decompression illness [20], HBOT treats the cerebral RI from bubble passage through the brain blood vessels, not the treatment of bubbles themselves [20]. It is the dominant effect of HBOT in six of the fifteen typically reimbursed indications for HBOT in the U.S. today: decompression sickness, air embolism, carbon monoxide poisoning, compromised flaps and grafts, acute arterial insufficiency, and thermal burns [4]. It is a generic effect [24] that would impact many emergency conditions and iatrogenic diseases that involve tissue injury or interruption of blood supply, particularly when applied immediately after the iatrogenic error [25,26].
For known, expected, and predictable iatrogenic harm, HBOT can mitigate RI before the iatrogenic insult is delivered. Now known as pre-conditioning this was first demonstrated in acute carbon monoxide poisoning [22] where a single pre-carbon monoxide HBOT exposure mitigated the severity of RI. For mild stresses/insults/injuries, considered as hormetic stresses [27], HBOT pre-conditioning is not a mandate. Such stresses alone may generate beneficial effects as embodied by Friedrich Nietzsche's principle [28], "What doesn't kill you makes you stronger." If an ischemic, hypoxic, mechanical, or other stress/insult/injury exceeds this hormetic level, one to five HBOTs prior to the insult pre-conditions the organism/human to experience less damage from the insult [29]. This has been demonstrated in reversible models of ischemia/reperfusion injury and now in an extensive literature on the subject [30].
Alex, et al. [31] utilized two pre-conditioning HBOTs the night before cardiac bypass surgery to significantly decrease cognitive injury. Applied to both higher risk and healthy patients before any operation that involves planned interruption of blood supple [e.g., arterial bypass surgeries, cardiac bypass surgeries, extremity tourniquet procedures (vascular or orthopedic), organ transplantation, etc.], urgent/emergent procedures with interruption of blood supply (e.g., traumatic repair of limbs, re-attachment of severed parts, flap and graft procedures, crush injuries, severe traumatic injuries, etc.) or substantial risk of blood loss/hypotension, HBOT has the potential to and can mitigate the effects of trauma, surgical injury, and surgical complication [32].
2. **Addressing the country's mental health crisi**s: HBOT's benefit to mental health is best understood in the context of the biological model of psychiatry [33]. If psychiatric diseases result from organic disturbances of the brain and some of these disturbances are considered to be due to stress/insults/wounding conditions, they are potentially responsive to HBOT. This is suggested in mild TBI HBOT studies where depression and/or anxiety were reduced [34-38]. In the same studies HBOT achieved significant PTSD symptom relief. A systematic review concluded, "In multiple randomized and randomized controlled clinical trials HBOT demonstrated statistically significant symptomatic improvements, Reliable Changes, or Clinically Significant Changes in patients with

PTSD symptoms or PTSD over a wide range of pressure and oxygen doses," using the U.S. Veterans Affairs grading system for PTSD [39]. Based on imaging findings, the study concluded that PTSD could no longer be considered strictly a psychiatric disease. The application of HBOT to Americans with PTSD could immediately impact the mental health crisis in America, particularly for our veterans who are in the midst of a suicide epidemic.

A greater immediate impact of HBOT could be achieved with another "psychiatric" disorder, persistent post-concussion syndrome [40]. Despite inarguable evidence of physical damage to the brain in mild TBI, particularly to the white matter [41-49], but also gray matter [43-45,50,51], persistent post-concussion syndrome is defined as a psychiatric condition [40]. A systematic review concluded that HBOT for mTBI PPCS was Level I evidence and a Grade A Practice Recommendation [52]. Preceding this literature, three randomized trials from the 1970s to 2013 have shown that HBOT reduces the mortality in acute severe TBI by 50% [53-55]. While these studies should have changed the standard of care, this application awaits the results of the current multi-center trial of HBOT in acute severe TBI [56].

3. **Combating diabetes and metabolic disorders:** HBOT has demonstrated significant benefit in the most common hospital admission diagnosis for diabetics, diabetic foot wounds. Diabetic foot wounds often lead to major lower limb amputations which are associated with a 3-year mortality of 64-71% [57]. In multiple controlled trials, HBOT has demonstrated wound healing and reduction in major amputations [58]. The latter effect was the basis for the application to CMS in 11/2001 and the decision by CMS to reimburse HBOT treatment of diabetic foot ulcers (DFUs) [59]. Unfortunately, the population that has benefited the least from this indication is the veteran population. Between 2002-2022, less than 6.36% of veterans undergoing lower limb amputation for diabetic foot ulcers received HBOT [57]. If applied according to CMS rules, HBOT could have an immediate impact on the health of our veteran population with DFUs.
4. **Mitigating the rise of autoimmune diseases:** Mitigating the rise of autoimmune disease requires identifying and reducing/eliminating the causes of autoimmune disease which are likely the lifelong environmental chemical and toxin exposures to/ingestions by humans. Eliminating these causes involves a concerted environmental, industrial, corporate, agricultural, government, and individual personal effort that will take years to achieve. In the meantime, HBOT can mitigate autoimmune and immune system disorders characterized by chronic focal or systemic inflammation. In gene experiments (vide supra), HBOT has demonstrated wide-ranging effects on immunomodulatory genes in normal non-diseased cells [60-62] and on inflammation in autoimmune and inflammatory disorders [63-68]. Given the contribution of inflammation to 8 of the top 10 leading causes of death in the U.S.[69], HBOT has the potential to treat a long list of diseases and contribute to The New Vision.

Important inflammatory diseases in which HBOT could make a significant contribution to the New Vision are acute severe COVID infection and Post-COVID Syndrome. Unbeknownst to the current generation of doctors, HBOT's introduction to the United States occurred during the Spanish Flu Pandemic when HBOT was successfully delivered to moribund dying Spanish Flu patients [2,70]. The HBOT benefit was due to treatment of the intense inflammatory components of Spanish Flu. A similar responsiveness to acute COVID-19 infection was first demonstrated in Wuhan [71,72], subsequently replicated by others [73], and extended to patients with Post-COVID Syndrome [74,75] and brain fog [76]. A recent study showed that over 55% of Americans with prior COVID infection have 3 or more persistent symptoms at least one month after

COVID 19 infection [77]. With no acknowledged effective treatment options, HBOT could significantly impact the health of these patients and contribute to the New Vision.

5. **Additional consideration of importance--HBOT application to chronic neurological disorders:** Many neurological disorders, e.g., TBI (vide supra), birth injury/asphyxia, and cerebral palsy, share the same pathogenesis and pathophysiology as the traditional HBOT-treated wounding and inflammatory conditions. Application of one HBOT in 1963 to neonates who were born not breathing and failed resuscitation resulted in resuscitation and discharge "apparently well" of 54% of the infants [78]. HBOT's treatment of reperfusion injury was likely the determining factor. Subsequent studies [79,80] have supported this 1963 study and argue for the treatment of apneic newborns.
For chronic pediatric brain injury, specifically cerebral palsy, the evidence is even more compelling [81,82,83]. A comparative effectiveness study of all traditional therapies found HBOT to be four times as effective as the average effect of all other therapies on motor function in CP children [84]. In addition, the HBOT studies demonstrated significant improvement in other functional domains, including cognition. These studies and the ones on birth injury indicate that HBOT could have an impact on acute and chronic pediatric neurological disease and contribute to the New Vision.

In summary, hyperbaric oxygen therapy is a dual-component therapy consisting of increased pressure and increased pressure of oxygen that takes advantage of all living organisms' sensitivity to pressure and oxygen. It has epigenetic effects on normal tissue and diseases, namely, growth of tissue, inhibition of inflammation, inhibition of cell death, and healing of wounds. Because of these effects, scientific studies have demonstrated HBOT benefit in a wide range of human diseases, only a fraction of which are currently treated with this therapy. Based on the science, application to these diseases and more can immediately impact the four cornerstones of the New Vision to *Make America Healthy Again.*

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Conflict of Interest: Paul G. Harch, M.D. is the owner of Harch Hyperbarics, Inc. an S-Corporation, that is the vehicle for his private practice of hyperbaric medicine.

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