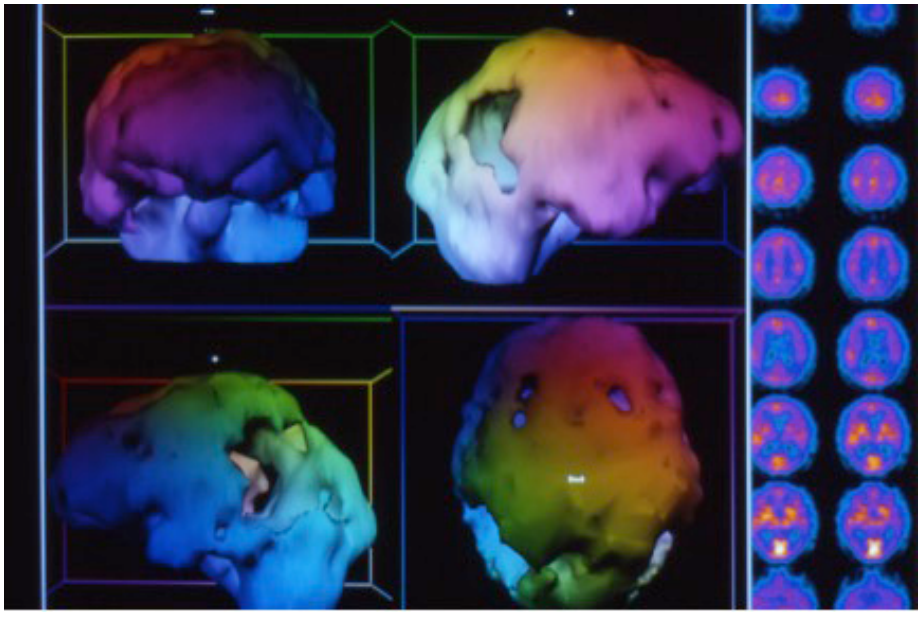
Oxygen and Pressure Epigenetics: Understanding Hyperbaric Oxygen Therapy After 355 Years as the Oldest Gene Therapy Known to Man

by Paul G. Harch, MD

Despite the "Decade of the Brain" from 1990-2000[1] and all the advances of modern medicine, treatment of the most common neurological diseases (traumatic brain injury, stroke, and dementia) has made minimal progress in the last 100 years. In 2017 Alzheimer's Dementia alone accounts for 5.4 million cases in the U.S.[2] Total costs for dementia are estimated to be $259 million this year.[2] The numbers will burgeon in the decades ahead as the Baby Boomers' demographic and the excesses of their earlier years pay a negative dividend.

Imagine for a moment a treatment that generically addresses/treats the underlying pathophysiology of traumatic brain injury (TBI), concussion, stroke, dementia, and many other neurological and systemic diseases, a treatment that not only restores reserve capacity,[3] but stimulates repair and regrowth of tissue, a treatment that gives people back their lives.

Figure 1. Pre-HBOT, SPECT brain blood flow imaging transverse slices and four-view three-dimensional surface reconstruction of 58-year-old male with Alzheimer's disease. Color scheme for slices is white, yellow, orange, purple, blue, and black from highest to lowest blood flow. Color scheme for three-dimensional surface reconstructions is aesthetic. Three-dimensional views are top row, left to right: frontal and right lateral; bottom row, left to right: left lateral and top of head. Defects or holes in the surface represent significant relative reductions in blood flow. Note primary defects in parietal/occipital/temporal watershed regions.



Figures 1-4 feature the SPECT brain blood flow scans of the first Alzheimer's patient treated with oxygen and pressure epigenetics. On a challenge from neurologists at the University of Oklahoma School of Medicine, a 58-year-old man was referred for treatment 5.5 years after the diagnosis of Alzheimer's disease. Having failed multiple treatments and shown minimal symptomatic improvement on rivastigmine, the scans document the typical posterior watershed areas of damage in Alzheimer's and the dramatic improvement in regional brain blood flow after one, 40, and 80 hyperbaric oxygen therapy (HBOT) treatments. Simultaneously, the patient's symptoms, quality of life, and Folstein Mini-Mental Status Exam score improved (from 9 to 13); and formal cognitive memory testing by university neuropsychologists recorded the first improvement in their multi-year testing sequence. The case was reported to the US Congress in 2002, along with 14 other cases of chronic traumatic brain injury, substance abuse, mental retardation, cerebral palsy, stroke, alcoholism, carbon monoxide poisoning, shaken baby, and autism.[4]

Since 2001 this author has treated nearly 1,000 cases of chronic neurological injury spread across 80 or more neurological diagnoses. This

includes eight additional Alzheimer's cases, and over 60 cases of cognitive decline/dementia of a variety of causes, including this author's mother, whose life and quality of life were prolonged six years with oxygen and pressure epigenetic therapy.[5] How can 80 intermittent exposures to increased pressure and hyperoxia improve neurocognitive function in a patient with a terminal neurodegenerative disease? How can 14 other cases with a variety of untreatable chronic neurological diseases respond similarly? The answer to this question begs the question of "What is hyperbaric oxygen therapy?" The answer given to this author by his medical school resident was the answer given to his entire generation of physicians: "… a type of oxygen therapy, it's performed in chambers, and it's worthless, unscientific, been thoroughly disproven, charlatanism, snake oil sales, and fraud."[5] Eight years later in a diving medicine practice, this author found this wasn't true. The correct answer has vexed the medical profession for 355 years, but will only be apparent after a quick review of the most misunderstood therapy in medicine.

Hyperbaric therapy originated in England in 1662[6] and, through the 1930s, consisted exclusively of compressed air. The breadth of its application was reflected in an 1877 review by Arntzenius which featured 300 references.[7] Oxygen was added to air decompression treatment tables by the US Navy in the late 1930s, and Dutch surgeons started using high pressure oxygen for surgeries, infections, and poisonings in the 1950s to spawn the modern era of hyperbaric oxygen therapy.[5] To organize the new field, establish credibility, and gain reimbursement, early hyperbaric physicians identified a list of purportedly scientifically proven diagnoses that were adopted by the FDA (Table 1).[8] The foundation of this list was an arbitrary unscientific definition of HBOT.[9] That definition has confused the scientific community, Food and Drug Administration, Medicare, medical insurance companies, and lay public, and stymied the understanding and advance of the therapy ever since:

> Hyperbaric oxygen (HBO_2) treatment, in which a patient breathes 100% oxygen intermittently while inside a treatment chamber at a pressure higher than sea level pressure (i.e., > 1 atmosphere absolute; atm abs), can be viewed as the new application of an old, established technology to help resolve certain recalcitrant, expensive, or otherwise hopeless medical problems…pressurization should be to 1.4 atm abs or higher.[9]

The definition omitted the 300+ year contribution of pressurized air[6] and lacked any evidence that 1.4 ATA (atmospheres absolute) of pressure was the minimum pressure requirement for HBOT, i.e., 1.399 ATA or less pressure was not. In addition, "certain recalcitrant, expensive, and otherwise hopeless" describes nearly all chronic and most acute medical conditions, yet the list of "certain" diagnoses is 48 in

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Figure 2. After one HBOT, SPECT brain blood flow imaging transverse slices and four-view three-dimensional surface reconstruction of 58-year-old male with Alzheimer's disease.

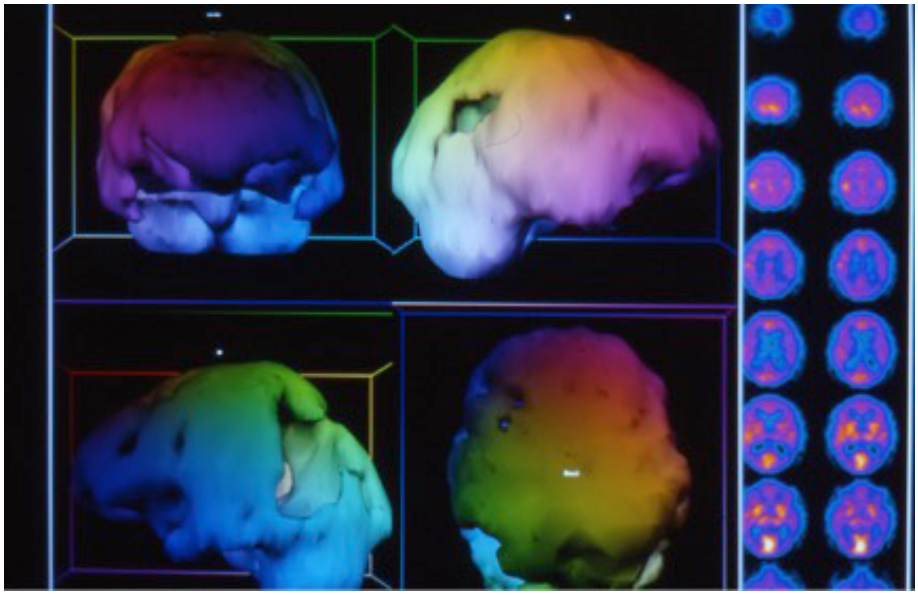
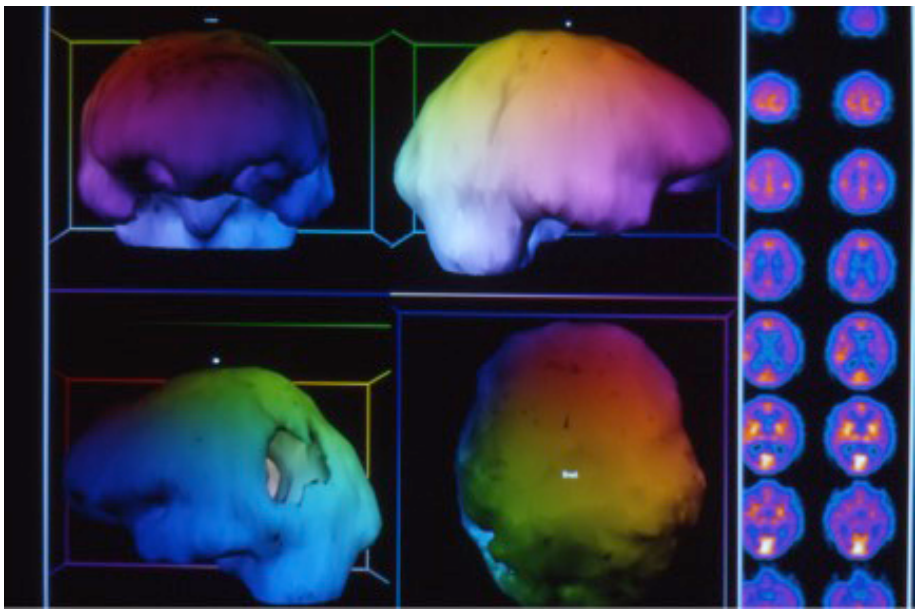


Figure 3. After 40 HBOTs, SPECT brain blood flow imaging transverse slices and four-view three-dimensional surface reconstruction of 58-year-old male with Alzheimer's disease.



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China, and more than 60 in Russia.[10] This definition of HBOT appears to change as it crosses national borders, yet scientific principles don't and shouldn't. Sir Isaac Newton's apple falls the same way in the US as it does in Russia, not the opposite direction.

Table 1. FDA-Cleared Indications for Hyperbaric Oxygen Therapy

1. Air or Gas Embolism
2. Carbon Monoxide Poisoning and Smoke Inhalation, Carbon Monoxide Complicated by Cyanide Poisoning
3. Clostridial Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome, and Other Acute Traumatic Ischemias
5. Decompression Sickness
6. Enhancement of Healing in Selected Problem Wounds
7. Exceptional Blood Loss (Anemia)
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections (Subcutaneous Tissue, Muscle, Fascia)
10. Osteomyelitis (Refractory)
11. Radiation Tissue Damage (Osteoradionecrosis)
12. Skin Grafts and Flaps (Compromised)
13. Thermal Burns

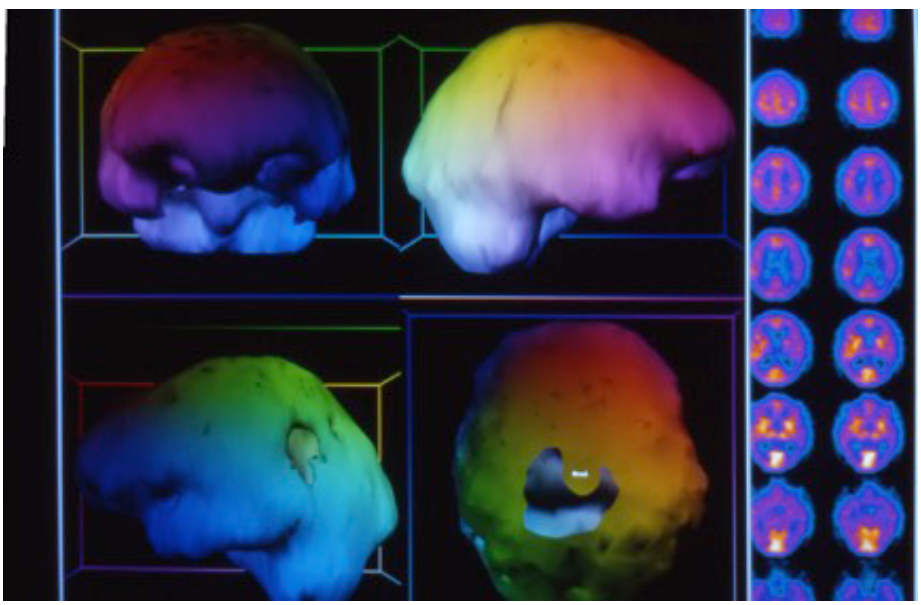
The confusion over this mis-definition and Table 1 is that no physician has been able to connect the dots …until now. In 1999, HBOT was redefined scientifically as "…a medical treatment that uses high pressure oxygen as a drug by fully enclosing a person or animal in a pressure vessel and then adjusting the dose of the drug to treat pathophysiologic processes of the diseases."[11] HBOT had been shown in multiple animal species to have profound effects on acute and chronic disease pathophysiology.[9] It was felt that the intermittent exposure to increased pressure of oxygen acted to ameliorate acute disease pathophysiology and the repetitive application in chronic conditions to have trophic effects, i.e., grow new tissue.

This definition, however, was inadequate. It still did not explain the 300+ years of pressurized air,[6,7] the Russian experience with very low doses of hyperbaric therapy,[12] nor the confusing HBOT cerebral palsy study of 2001 where 1.3 atmospheres absolute of air (9.9 feet of seawater pressure, the depth of a swimming pool) improved children with cerebral palsy (CP).[13] All of these examples feature elevated pressures with minimal elevations in oxygen. The FDA inadvertently clarified the matter in their 2012 response to this author's Investigational New Drug Exemption (IND) application: "… we consider your intervention to be a combination therapy, the constituents of which are hyperbaric treatment and hyperoxic treatment. Each of these constituents has the potential to contribute independently to the overall therapeutic effect…" This suggested for the first time in the modern history of hyperbaric medicine the possible contribution of hydrostatic pressure to the clinical effects of HBOT.

A quick investigation revealed 70 years of published research demonstrating the responsiveness of living organisms to the slightest elevations in atmospheric pressure that began within as little as one minute of pressurization.[14] Somehow, this treasure trove of literature escaped the purview of the entire modern clinical hyperbaric medicine field. Pressures from 1.0015 to 1.26 ATA delivered to human and animal cells for 15 minutes or longer have caused the elaboration of a wide variety of bioactive proteins and stimulated cell proliferation.[15] In other words, hydrostatic pressure effects were an essential component of hyperbaric therapy, and they are elicited by very small increases in pressure.

Acknowledging this wide range of hyperbaric and hyperoxic bioactivity, the controversial applications to CP,[13] autism,[16] mild traumatic brain injury/persistent post-concussion syndrome (PPCS),[17] PPCS with post-traumatic stress disorder,[18] and other diagnoses become understandable as multi-dosing hyperbaric therapy studies have demonstrated effectiveness of some doses of hyperbaric therapy, ineffectiveness of others, and toxicity of others.[15,19] In particular, all of these studies have demonstrated the benefit of hyperbaric therapy in the low pressure/low hyperoxic range. This low-dosing range was reinforced by

Figure 4. After 80 HBOTs, SPECT brain blood flow imaging transverse slices and four-view three-dimensional surface reconstruction of 58-year-old male with Alzheimer's disease. Clear area in top-of-head view in right lower quadrant is artifact due to edge cutoff of camera field of view.



the recent publication of a two-year-old drowned girl who experienced dramatic neurological recovery and global regrowth of brain tissue after three months of normobaric oxygen and hyperbaric oxygen therapy.[20]

The question remained, however, how do repetitive administrations of intermittent increases in pressure and oxygen reverse pathophysiology and stimulate tissue growth? Tissue growth requires replication of DNA. In 1997, Siddiqui et al argued that the oxygen component of HBOT was a DNA signaling agent.[21] Multiple publications confirmed this concept in the next 11 years,[22-30] culminating in the demonstration that a single HBOT at the pressure used for diabetic foot wounds and radiation wounds up- or down-regulated the expression of 8,101[31] of the known 19-20,000[32] protein-coding genes in the human genome. The largest clusters of upregulated genes were the anti-inflammatory genes and those that coded for growth and repair hormone, and the largest clusters of downregulated genes were the pro-inflammatory genes and apoptotic genes. Further work showed the differential gene effects of pressure and oxygen,[33] whereby different and similar clusters of neuronal genes are affected by different pressures and different amounts of hyperoxia.[34] In essence, during hyperbaric therapy physicians are playing a symphony with patients' gene expression, the music of which is determined by the various pressures and amounts of hyperoxia to which the patient is exposed.

Summing up the current understanding of this 355-year-old therapy, HBOT appears to be an epigenetic therapy in the broad sense of the original definition of Waddington: "…the branch of biology which studies all molecular pathways modulating the expression of a genotype into a particular phenotype."[35] The combination of hyperoxia and increased pressure are acting at the epigenetic level to differentially and temporarily alter gene expression and suppression of over 40% of all of our protein-coding genes. The net effects are permanent tropism and tissue repair and temporary and permanent inhibition of inflammation and apoptosis.[9,31,36-8] By mechanisms involving oxygen-sensitive gated membrane ion channels[39] and pressure-induced strain on cell and mitochondrial membranes,[14,40] hyperbaric pressure and hyperoxia are two organically, and naturally, manipulating, ubiquitous natural-occurring agents that effect salutary changes in disease at the epigenetic level. Essentially, this is the oldest, most pervasive and panoramic gene therapy finally known to mankind.

Viewed as a gene therapy, this discussion comes full circle to the constrained list of clinical applications in the United States and begs the question of what other diagnoses may be responsive to oxygen and pressure epigenetics. Controlled trials exist for many diagnoses, including idiopathic sudden sensorineural hearing loss,[41] acute severe traumatic brain injury,[42] acute myocardial ischemia,[43] CP,[13] autism,[16] prevention of post-coronary artery bypass cognitive decline,[44] multiple sclerosis,[45] avascular necrosis,[46] fibromyalgia,[47] complex regional pain syndrome,[48] and vascular dementia.[49] This last study is most exciting because it confirms in a controlled trial the author's previously mentioned 31-year experience treating diagnoses of cognitive decline, premature aging, and dementia. The possibilities and impact of treatment of these diagnoses of aging are inestimable. Considered in combination with all the other potentially treatable diagnoses based on the mechanism of oxygen and pressure epigenetics, the 132 conditions listed in the 1987 critique of HBOT, "A Therapy in Search of a Disease,"[50] may in fact be a limited list.

In conclusion, hyperbaric therapy is the use of increased pressure and hyperoxia to treat diseases through temporary gene expression and suppression. After 355 years, we finally understand hyperbaric therapy as the most long-standing, panoramic, and effective gene therapy known to man; yet the therapy is in its infancy of dose exploration and disease application.

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Beginning with brain-injured divers and boxers in 1989, he applied his protocol to the first HBOT-treated cerebral palsy and autistic children in this country and multiple other cerebral disorders, including most recently a subacute drowned child (*Medical Gas Research*. March 2017). He has successfully treated US servicemen with TBI and PTSD, publishing the latest findings in *Medical Gas Research,* October 2017. His studies in brain-injured veterans have continued with a randomized trial funded by a Louisiana-generated congressional appropriation. The early case experience was confirmed in an animal model of chronic traumatic brain injury that was published in *Brain Research* in October 2007.

He has presented his research seven times to the US Congress and been nominated for the NIH Director's Pioneer Award. In April 2007, he published *The Oxygen Revolution* with co-author Virginia McCullough. This groundbreaking book, which has been released in its third updated edition in May 2016, explains HBOT as an epigenetic gene therapy and its projected revolutionary effects on medicine and neurology.