

Review

The On/Off History of Hydrogen in Medicine: Will the Interest Persist This Time Around?

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Abstract: Over 2000 publications including more than 100 human studies seem to indicate that humans have only recently benefited from or known about the medical effects of H₂ within the past 15 years. However, we have unknowingly benefited from H₂ since the dawn of time, from H₂-producing bacteria to the use of naturally occurring hydrogen-rich waters. Moreover, the first writings on the therapeutic effects of H₂ date to around 1793. Since then, papers appeared sporadically in the literature every few decades but never exploded until Ohsawa et al. again demonstrated hydrogen's therapeutic effects in 2007. This landmark paper appears to have been the spark that ignited the medical interest in hydrogen. Although H₂ was used in the 1880s to locate intestinal perforations, in the 1940s in deep sea diving, and in the 1960s to measure blood flow, H₂ was largely viewed as biologically inert. This review highlights the history of hydrogen in the genesis/evolution of life and its medicinal and non-medicinal use in humans. Although hydrogen medicine has a long and erratic history, perhaps future history will show that, this time around, these 15 years of ignited interest resulted in a self-sustaining explosion of its unique medical effects.

Keywords: antioxidants; COVID-19; diving; hydrogen-rich water; hydroxyl radicals; molecular hydrogen; neurodegenerative diseases



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1. Introduction

Molecular hydrogen (H₂ gas) is well known for its many industrial uses [1,2], and has been essentially considered to be biologically inert, as well as being relatively insoluble. However, recent biomedical research shows that hydrogen has great potential as a therapeutic molecule [3]. Although the research is still in its relative infancy, over 1300 publications suggest that it has potential therapeutic effects in over 170 different human and animal disease models, and in essentially every organ of the human body [4]. Although it is already known that other gases, such as nitric oxide [5] hydrogen sulfide [6], and carbon monoxide [7] have significant biological effects, hydrogen gas came to the forefront of medical gas research in 2007, when an article published in *Nature Medicine* [8] demonstrated its neuroprotective effects following middle cerebral artery occlusion. Fewer than 50 articles were published regarding hydrogen as potential medical gas pre-2007, compared to over 2000 articles within the past 12 years. Figure 1 illustrates this rather exponential increase in publications on molecular hydrogen. However, the primary targets and molecular mechanisms of hydrogen gas remain elusive [9].

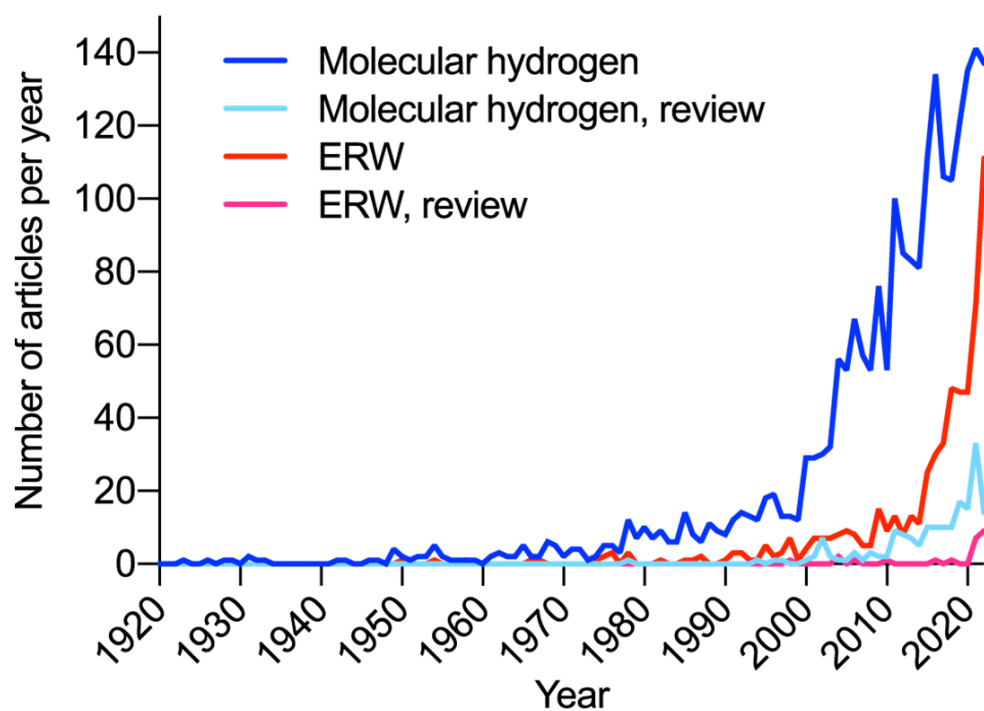


Figure 1. Articles Published Relating to Molecular Hydrogen and Electrolyzed Reduced Water (ERW). Articles with “molecular hydrogen” in the title but not “hydrogen bonding” were counted each year. Similarly, articles with “electrolyzed reduced water”, “alkaline water”, or “alkaline ionized water” in the title or abstract were counted each year. Note that some searched articles are not directly relevant to the biological/medical effects of H₂.

2. Hydrogen History

There appear to be five different areas involving hydrogen research that converged following the announcement of Oshawa et al. in 2007 [8] that molecular hydrogen could exert positive biological effects. These areas include the uses of hydrogen in (i) the genesis and evolution of life, (ii) humans for non-medicinal purposes, (iii) natural “miracle” waters, (iv) electrolyzed reduced water, and (v) therapeutic and medical applications. Figure 2 shows an annotated timeline regarding hydrogen history.

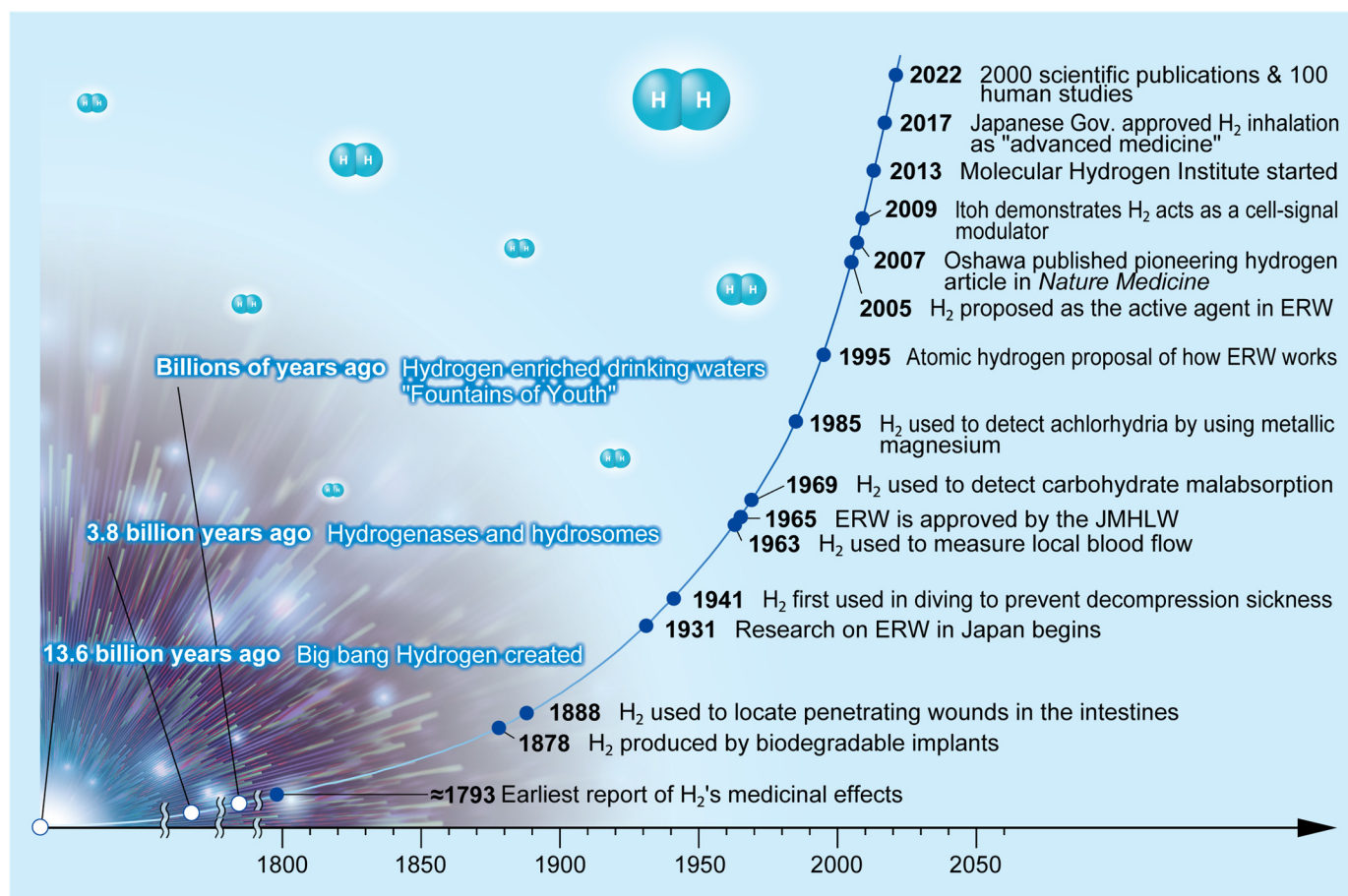


Figure 2. Timeline of important events involving hydrogen as an important molecule. ERW (electrolyzed reduced water), JMHLW (Japanese Ministry of Health Labor and Welfare).

3. Hydrogen in the Genesis and Evolution of Life and Effects in Plants

3.1. Hydrogen Chemistry

Hydrogen in the atomic form is the simplest element, consisting of only one electron and one proton, but it exists primarily in its diatomic form (H₂). It is a tasteless, odorless, colorless, and non-toxic nonmetallic gas [10]. Hydrogen is at the center of the prevailing cosmological model that describes the early development of the universe [11] as well as the origin of life itself [12,13].

By fusion hydrogen is converted into helium, which then undergoes the triple- α process to form the lightest biogenic element, carbon. Biologically relevant elements, such as oxygen, nitrogen, sulfur, and phosphorus, as well as the other elements, were formed in a similar manner. In an exothermic reaction, hydrogen reduces these elements to form the important molecules ammonia (NH₃), methane (CH₄), water (H₂O), cyanide (HCN), and hydrogen sulfide (H₂S) [14]. Indeed, hydrogen can be considered to be the ancestor of not only the elements of the universe but also the molecules of life.

Hydrogen has rich chemistry and can readily participate in oxidation–reduction reactions (e.g., hydride transfer, electron acceptor or donor with dehydrogenases, and hydrogenation of alkenes in the presence of a catalyst), and is central to the definition of Brønsted–Lowry acid–base reactions (i.e., donating a hydrogen cation, “H⁺”, or accepting one to be an acid or a base, respectively).

Molecular hydrogen is the most energy dense molecule by mass in the universe, being over three times more energy dense than gasoline [15]. It is interesting that given the fact that a ratio between oxidation and reduction is required for the existence of life, that the two elements that characterize these extremes are oxygen and hydrogen, which react together to produce the universal solvent H₂O, which allows life to exist.

Over the years much attention has been given to oxygen, both in its role for life and in its role for death by forming cytotoxic reactive oxygen species (ROS) [16]. ROS have been implicated in the pathogenesis and progression of virtually every disease [17]. Nevertheless, research also shows that ROS existence is pivotal for normal cellular function, cell signaling, protein folding, cell proliferation, etc. [18]. Thus, it is the dysregulation of ROS, too much or too little, that is the problem [19]. This can lead to conditions referred to oxidative stress (too much oxidation) or the opposite, i.e., reductive stress [20]. The intracellular redox activity is therefore a balance, impinged upon by the accumulation of ROS, and maintained by redox active molecules such as glutathione (as in the GSH:GSSG couple). Perturbation of this redox balance can lead to disease or cell death, often through apoptotic pathways [21]. It is into this complex web of redox molecules that H₂ must fit if it has effects on biological systems.

3.2. Hydrogen and Genesis and Evolution of Life

Cellular redox homeostasis is maintained by various dehydrogenase enzymes [22]. The Ni/Fe hydrogen dehydrogenase (hydrogenase) enzyme can catalyze the reversible oxidation of hydrogen gas ($H_2 \leftrightarrow 2H^+ + 2e^-$). It is amongst the oldest enzymes (3.8 billion years old), which demonstrates that life had to develop a way to activate molecular hydrogen at ambient temperature and pH [23]. Perhaps this ability was needed to help maintain the balance between oxidation and reduction [24–26]. As an example, generation of H₂ and the concomitant reduction of oxidation are important for the survival of *Klebsiella pneumonia* in the oral cavity [27].

Furthermore, according to the various theories of eukaryotic genesis (e.g., endosymbiotic theory, hydrogen hypothesis, etc., which involve hydrogenases, hydrosomes, and mitochondria), hydrogen has been intimately involved throughout the origins and evolution of life [12,28]. Perhaps hydrogen gas served as a signaling molecule in these early organisms, and, although they lost their ability to produce hydrogen gas, some of hydrogen's targets and functions are conserved [29]. Although humans lack the hydrogenase enzyme, recent research shows that hydrogenases are ubiquitously distributed among many lower eukaryotes [30]. Indeed, genes that bear the hallmark signature of the Fe-hydrogenase are found in the genomes of higher eukaryotes including humans [30]. The presence of basal levels of hydrogen in the human body may suggest that it has a physiological role [31]. The adoption of what would be commonly available molecules in the early evolution of life, some of which would have even been toxic, into the normal signaling roles in cells has been noted for ROS and reactive nitrogen species such as nitric oxide [32], so it is not much a leap to suggest that hydrogen was also adopted for positive uses.

It is likely that if hydrogen gas were completely removed, then the physiological significance of hydrogen gas would also be lost; however, due to the presence of certain bacteria, neither hydrogen gas nor its molecular targets may have been fully eliminated. Indeed, many plants, insects, animals, and humans have developed a mutualistic relationship with hydrogen-producing bacteria [33–36]. If this hypothesis is true, then exogenous hydrogen should still exert a biological effect on those organisms.

3.3. Hydrogen in Plants and Agriculture

As already discussed, many, insects, animals, and humans have developed a mutualistic relationship with hydrogen-producing bacteria [33,36], and plants too seem to be affected by the presence of H₂. It has recently been found that exogenous hydrogen exerts a protective effect on a number of different plants including alfalfa [37], arabidopsis [38], cucumber [39], rice [40], and radish sprouts [41].

Preliminary evidence was reported that the plasma membrane vesicles of *Vigna radiata* hypocotyls and *Capsicum annuum* stems can both oxidize and produce molecular hydrogen [42]. A proposed "hydrogenase-like complex" in the plasma membrane may act as an electron/proton donor by oxidation of H₂ or an electron/proton acceptor by producing H₂. It is postulated that this function might help to maintain the plant redox homeostasis, and

the observed effects of H₂ on plants may be mediated by a bidirectional H₂ metabolism activity [42].

Despite the unknown exact molecular mechanisms of molecular hydrogen in plants, the beneficial effects have continued to be reported. In a review article [43], we summarized some of the studies showing that the treatment of plants and plant products with H₂ alleviates plant stress and slows crop senescence. Many of these effects appear to be mediated by the alteration of the antioxidant capacity of plant cells [43]. More recently, reviews of the use of H₂ in agriculture as well as in postharvest storage have appeared [43–45], and the number of papers on hydrogen effects in plants has escalated (Figure 3).

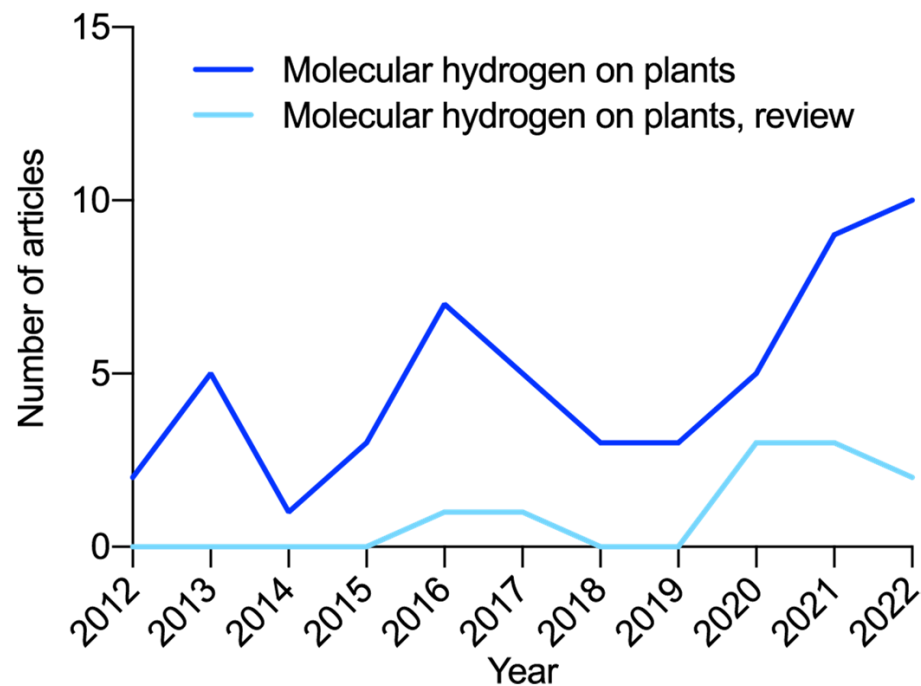


Figure 3. Articles Published Relating to Molecular Hydrogen in Plants. Articles with both “molecular hydrogen” and “plant” either in the title or abstract were counted since 2012 when the effect of H₂ on plants was first published [46]. Note that some searched articles are not directly relevant to the effects of H₂ on plants.

4. Hydrogen Use in Humans for Non-Medicinal Purposes

There are six primary practices involving hydrogen gas and humans that have been occurring for many years, without always acknowledging hydrogen as a medically or biologically active gas.

4.1. Biodegradable Implants

In 1878, magnesium metal gained attention in the orthopedic and biomedical engineering fields as a promising candidate for biodegradable implants, such as wires, plates, sheets, rods, screws, and pegs [47]. The magnesium implantation slowly dissolves in the body releasing hydrogen gas and magnesium ions ($\text{Mg} + 2\text{H}_2\text{O} \rightarrow \text{Mg}(\text{OH}^-)_2 + \text{H}_2$). Magnesium alloy implants are still being researched today [47–49]. Perhaps a previously unknown benefit of these implants is the release of hydrogen gas [50], which may help explain the regeneration of nerves and only mild inflammation of tissues [49]. Indeed, magnesium-based implants have been shown to have anti-tumor activity by inducing the p53-mediated lysosome–mitochondria apoptosis signaling pathway [51].

4.2. Bodily Wounds

Molecular hydrogen was used in 1888 to locate penetrating wounds (i.e., gunshot and knife wounds) in the gastro-intestinal tract by rectal insufflation [52,53]. This was a major medical advancement because if there was a penetrating wound of the GI tract, then it was inevitably fatal unless treated by suture. However, confirming that there really was a hole was risky. Dr. Senn who developed this method of using H₂ gas reasoned that a wound in the GI tract should be located in the same method as how a plumber locates a leak in a pipe. Dr. Senn performed several animal and human experiments showing the efficacy and safety of this method. He observed that it is more difficult to inflate the alimentary canal from the mouth to the anus compared from the anus to the mouth. The technique involved injecting H₂ from an elastic syringe connected to a balloon full of hydrogen gas. The inflation was traceable by percussion and manipulation. Rectal insufflation would cause gas bubbles to accumulate outside of the intestines around the wound. In order to prove that the bubbles were from the H₂, the surgeon would then light a match and ignite the hydrogen. There would be a slight explosive effect and would then burn with a characteristic blue flame. The burning of the hydrogen gas was encouraged for diagnostic and aseptic purposes. Rectal insufflation of hydrogen gas was shown to be an infallible test in every instance when the apparatus was working correctly. It was also noted that hydrogen gas was devoid of any toxic properties, and it was nonirritating when in contact with the most sensitive tissues [53].

4.3. Diving

In 1941, it was shown that breathing a 97% hydrogen and 3% oxygen mixture at 10 atm was well tolerated and safe [54]. This resulted in the use of hydrogen in deep sea diving to prevent decompression sickness in 1943 by the Swedish Royal Navy [55,56] and has continued to be used since. Often a mixture of oxygen and helium (e.g., Heliox, Trimix [57]) is used for this purpose and is not flammable. However, despite its inherent flammability, since H₂ is the lightest gas, half the weight of helium and less narcotic, it is a viable alternative to conventional diving gases. For example, hydreliox is a breathing gas mixture of hydrogen, helium, and oxygen [58]. In the case of very deep diving, Hydrox is used, which is a mixture of 96% hydrogen and 4% oxygen [59,60].

Because scuba diving increases oxidative stress [61], perhaps an additional and previously unknown benefit to using hydrogen in deep sea diving is its ability to reduce oxidative stress in these individuals [62]. Interestingly, hydrogen-rich saline was protective against decompression sickness in rats [63]. Diving would be an interesting model to further explore the effects of hydrogen on biological systems, if nothing else, to confirm hydrogen as a safe therapeutic agent.

4.4. Blood Flow

Hydrogen gas was again linked to medical applications in 1963 for the ease and accuracy in measuring local blood flow [64]. This concept has been used to study the blood flow of the cervix [65,66], gastric mucosa [67–70], kidneys [71,72], placenta and fetal tissue [73], liver [74], heart [75], spinal cord [76], pancreas [77,78], skin [79], and other uses [72,75,76,80–111]. It would be interesting if, due to the cell modulating effects of hydrogen gas, use of this molecule in these types of studies produced unexpected effects. Of course, other medical gases, such as nitric oxide and H₂S also have known effects on vasorelaxation and hence blood flow [112], with therapeutic agents being developed based on both of these molecules [113]. Again, the effects of H₂ would need to fit into this complex regulatory mechanism.

4.5. Malabsorption

Hydrogen gas is also produced by intestinal bacteria upon fermentation of non-digestible carbohydrates, which is estimated to be approximately 13.6 L/day [114]. Some of the hydrogen is removed by bacterial metabolism, about 14% is absorbed into the blood and exhaled via the lungs [115], and the rest is excreted as flatus [114]. However, the levels of H₂ production can be much higher in conditions of carbohydrate malabsorption. Thus, at least as early as 1969, the breath level of hydrogen gas has been used as a diagnostic indicator to test for carbohydrate malabsorption [116–122] and small intestinal bacterial overgrowth [123,124]. This type of testing is still commonly done today. Unfortunately, since increased breath hydrogen is diagnostically associated with an unfavorable condition, it might seem counterintuitive to realize that H₂ from intestinal bacteria also has many benefits [125], as discussed later (see: Section 7). However, it is interesting to note that increased levels of breath hydrogen gas may contribute to the longevity of Japanese centenarians [126].

4.6. Detecting Achlorhydria

Achlorhydria is the absence or reduction of hydrochloric acid in the digestion system, and as such can lead to a variety of medical conditions. Low stomach acid also results in impaired digestion including decreased absorption of certain vitamins, minerals, and nutrients, as well as increased propensity for digestive tract infections. In 1985, hydrogen gas production was used to assess achlorhydria by having patients ingest 10 to 200 mg of elemental magnesium and measuring the breath hydrogen produced by the reaction $Mg + 2HCl \rightarrow MgCl_2 + H_2$ [127–130].

5. Hydrogen in Natural “Healing” or “Curative” Spring Waters

The easiest and often most effective method for hydrogen administration is simply ingesting water containing dissolved hydrogen gas [131], referred to as hydrogen-rich water, making the water have potential medicinal-like properties.

The idea of “curative waters” seems to be prevalent throughout the history of mankind, including the writings of Hippocrates [132] and Herodotus with the concept of the Fountain of Youth [133]. Although much of the sentiments surrounding these so-called “healing waters” is that of folklore, magic, and pseudoscience [134], there are many cases where these waters have been scientifically documented to have therapeutic effects due to the water containing important constituents that many people were lacking (e.g., minerals) [135–137]; as well as gaseous hydrogen sulfide [6].

Investigations of some “curative waters” (e.g., Nordenau, Germany; Tlacote, Mexico; Hita Tenryosui, Japan; Nadone, India, etc.) have been reported to indeed exert therapeutic effects [138–140]. Intriguingly, there are reports that some of these waters contain small levels of dissolved molecular hydrogen [138,140–144]. In the late 1990s and early 2000s, a few procedural observational studies were performed on hundreds of diabetic patients who drank these claimed natural healing waters. The preliminary reports show that the patients had reduced levels of cholesterol, glucose, glycated hemoglobin (HbA1c), oxidative stress, serum creatinine, blood pressure, and exhibited other physiological health improvements [145–151]. After the realization that molecular hydrogen had therapeutic effects, it was conjectured that observed benefits from these so-called “curative waters” were due to the natural dissolved hydrogen in these waters [140].

The presence of molecular hydrogen in these waters may be a result of either abiotic origin (e.g., subsurface basalt-catalyzed water hydrolysis, serpentinization) [152–154], or biotic origin (e.g., hydrogen gas-producing bacteria) [155–159]. For example, H₂ produced between basalt and groundwater in the Columbia River Basalt aquifer at 1.2 km depth may serve as the energy source for methanogens [154]. Indeed, H₂-consuming methanogens thrive at depth of 200 m in Lidy Hot Springs, Idaho, USA [160]. Depending on the conditions of temperature and pressure, the concentration of hydrogen can range from >0.1 mM to well over 10 mM. This is significantly higher than normal saturation at standard

ambient temperature and pressure (i.e., 0.8 mM) [161]. However, although it is possible that the mentioned waters have molecular hydrogen, there is no credible evidence or details regarding their concentration. It is, therefore, unclear if these waters truly do (or did) contain clinically meaningful dissolved levels of molecular hydrogen [162]. It may be worth revisiting some of these potential spring waters using modern assaying techniques to ascertain if hydrogen is an active molecule accounting for any effects reported.

6. Hydrogen in Alkaline Ionized Water

The generation of hydrogen from electricity was accomplished as early as 1789 by Van Troostwijk and Deiman using an electrostatic generator [163]. Shortly after, Nicholson and Carlisle reported that an electrical current from the voltaic pile (the first battery) could induce the decomposition of water into hydrogen and oxygen (i.e., electricity + 2H₂O → H₂(g) + O₂(g)), a process called water electrolysis [164]. The hydrogen gas is formed at the cathode via proton (H⁺) reduction (2 H⁺(aq) + 2e⁻ → H₂(g)), and oxygen gas is formed at the anode by oxidation of hydroxide ions (2 H₂O(l) → O₂(g) + 4 H⁺(aq) + 4e⁻) [164]. A semi-permeable membrane that is impermeable to H⁺ and OH⁻ ions separates the anode from the cathode electrodes. The water at the cathode is alkaline and contains hydrogen gas, whereas the anode is acidic and contains oxygen gas (and often chlorine species due to voltage overpotential, which makes chloride ions more favorably discharged). Water produced at the cathode was referred to as “electrolyzed reduced water” (ERW) [138]. ERW has an alkaline pH, a negative oxidation reduction potential (ORP), and contains various levels of dissolved H₂ gas.

ERW research started in Japan in 1931 where it was initially applied to agriculture [140], and over the decades started to be viewed as beneficial for human consumption. Clinical studies were conducted to demonstrate safety so that these devices could be sold to the public. In 1965, under the Pharmaceutical Affairs Law, the Japanese Ministry of Health, Labor and Welfare approved these water electrolysis devices as safe and to be helpful with a variety of gastrointestinal symptoms [138,165–167]. However, as ERW became more popular, especially in the 1980s, anecdotal health claims continued to grow, which promoted investigative research in the 1990s [168]. Many cellular and animal studies confirmed that ERW had beneficial actions including antioxidant and anti-inflammatory effects [168]. However, it was not fully confirmed until after 2007 that molecular hydrogen was the exclusive agent in ERW responsible for these beneficial effects [168]. For the majority of ERW history, the involvement of molecular hydrogen was disregarded because H₂ was considered to be a biologically inert byproduct of electrolysis. Unfortunately, with no mechanistic explanation for why/how ERW is exerting these biological benefits, it becomes difficult to accept, and even more difficult to sell to customers. Regrettably, this contributed to a plethora of pseudoscientific conjectures used to explain the observed benefits of ERW. Some of these claims include (i) the alkaline pH to neutralize toxic waste, (ii) increased oxygen to energize the cells, (iii) altered water structure (e.g., microclusters) to increase cellular hydration, and (iv) a negative oxidation–reduction potential ORP indicating an antioxidant effect, but attributed to ideas such as solvated electrons, atomic hydrogen radicals, negative hydrogen ions, mineral hydrides, hydroxide ions, etc. [168].

As research on and interest in ERW continued, each claim was scrutinized and/or investigated, and one by one refuted until finally it was determined that hydrogen gas was the exclusive agent responsible for both the negative ORP [169] and the therapeutic effects [168]. Many articles have demonstrated that when H₂ gas is removed from ERW the therapeutic benefits are eliminated, as has been extensively reviewed [168]. Thus, despite benefits from ERW being observed at least as early as 1931, it was not known for over a half a century that these benefits were due to hydrogen gas. In fact, the majority of the early ERW articles did not report the concentration of H₂, which is a standard procedure now [168]. Unfortunately, many ERW proponents still do not recognize the importance of molecular hydrogen and continue promulgating some of the scientifically implausible and scientifically refuted concepts to explain ERW instead of focusing on the simplicity

of molecular hydrogen [168]. Importantly, many electrolysis devices and new hydrogen water technologies have now been developed that focus on producing high concentrations of molecular hydrogen without altering the pH [170]. These new technologies circumvent the potential safety concerns with ERW as well as the unique conditions that ERW devices require to make clinically relevant concentrations of dissolved H₂ [170].

7. Hydrogen in Therapeutic and Medical Applications

One of the earliest reports that hydrogen has medicinal properties was in the summer of 1793 by Thomas Beddoes (1760–1808), in a public letter he wrote to Erasmus Darwin, Charles Darwin's grandfather: *A letter to Erasmus Darwin, M.D. on a new method of treating pulmonary consumption, and some other diseases hitherto found incurable*. Beddoes was working at the Medical Pneumatic Institute in Bristol, UK. However, this paper was of limited scope.

In 1798 the Italian (from Naples) physicist Tiberius Cavallo (1749–1809), who moved to London in 1779, wrote a much longer treatise on his investigations on respiration: *An essay on the medicinal properties of factitious air. With an Appendix, on the Nature of Blood*. [171]. In this he discusses the therapeutic use of hydrogen. He reports that inhaling the hydrogen produced by the reaction of vitriolic acid (sulfuric acid) and iron is beneficial for inflammation of the lungs, coughs, and other disorders related to inflammation. He reported that in conditions where there is "tightness about the regions of the lungs and a hard cough", that a significant and "almost instantaneous relief has been frequently obtained by breathing a mixture of 4 quarts of hydrogen and 20 quarts of common air." [171].

Similar work was carried out under the instruction of Beddoes in Bristol by Humphry Davy (1778–1829: famous for the invention of the mining safety lamp, the Davy Lamp). In 1800 Davy wrote a very long treatise on the effects of nitrous oxide, and even contemplated its anesthetic effects. It was entitled *Researches, Chemical and Philosophical; chiefly concerning nitrous oxide, or dephlogisticated nitrous air, and its respiration*. As a "control" Davy used a variety of gases, including hydrogen which he compared to nitrous oxide (N₂O). He used his gases including hydrogen on a range of organisms, including several mammals, insects, amphibians, fish, snails, and worms, in what by today's standards would be considered inappropriate experiments. He also performed a wide range of self-experimentation, and gave his gases to friends and patients, some of whom were famous and renowned people. For more details of what Beddoes, Cavallo, and Davy said in their papers, see our "sister" review [Hancock and LeBaron: N.B. paper has been accepted, waiting for ref].

It was not until 1975 that the potential medical benefits of H₂ were again investigated, this time as a hyperbaric hydrogen treatment for skin cancer in mice [172]. Dole and colleagues of Baylor University and Texas A&M reported in the journal *Science* the significant positive biological effects of hyperbaric hydrogen treatment on skin cancer in mice [172]. However, in 1978, Roberts from the Southern Research Institute of Birmingham, Alabama was unable to recapture these remarkable results using solid transplantable tumors in mice [109].

In 1988, Neale presented a hypothesis that intestinal hydrogen gas produced via intestinal bacteria could be an effective antioxidant based on its standard reduction potential [173]. Nearly 20 years later the protective effects of hydrogen via intestinal microbiota were verified by a report from the Forsyth Institute in Boston MA and the University of Florida [174]. They found that reconstitution of intestinal microbiota with H₂-producing *E. coli*, but not H₂-deficient mutant *E. coli*, was protective against Concanavalin A-induced hepatitis. Anti-diabetic drugs, α -glucosidase inhibitors [175,176], turmeric [177], and milk [178] increase breath hydrogen concentrations in humans. The α -glucosidase inhibitor, acarbose, has unidentified additional effects on prevention of cardiovascular disease and hypertension [176]. Turmeric has long been known to have therapeutic potential for many human diseases [179]. The effects of these compounds may be accounted for by bacterial production of H₂. Additionally, ingestion of the dietary fiber pectin or high-amylose maize, which increases cecal hydrogen production, relieved ischemia-reperfusion injury in rats [180].

In 1996, David Jones wrote in the “Daedalus” column for *Nature*, described as one of the longest-running jokes on the scientific scene, about the benefits of hydrogen gas as an antioxidant against the hydroxyl radical and to help decrease inflammation. His parody continued about fictitious “DREADCO chemists” creating solubilized hydrogen beverages [181]. Many of the fictitious ideas regarding hydrogen in this column have now ironically, and perhaps fortuitously, become reality.

Jones’s column about hydrogen prompted Gharib and colleagues in 2001, to examine the effect of two weeks of 70% hydrogen gas on a mouse model of schistosomiasis-associated chronic liver inflammation [182]. The mice exhibited improved hemodynamics, increased antioxidant enzyme activities, increased nitric oxide synthase II activity, and decreased fibrosis and tumor necrosis factor- α levels.

Despite these favorable effects, there was very little interest in the biomedical applications of H₂, perhaps stemming from the fact that hyperbaric H₂ therapy was not a clinically viable option. This, due to the fact that H₂ gas is highly flammable in the presence of oxygen, which we obviously need to breath to sustain life. Thus, hydrogen therapy seemed clinically infeasible. However, the research increased exponentially after 2007, when Ohsawa and colleagues published their report in *Nature Medicine* [8]. They reported that a concentration of only 2–4% H₂ gas (which is below the flammability level) significantly reduced the cerebral infarct volumes in a rat model of ischemia-reperfusion injury induced by a middle cerebral artery occlusion. The authors further demonstrated that dissolved hydrogen in the media of cultured cells, at biologically feasible concentrations, selectively reduced levels of toxic hydroxyl radicals (\cdot OH), but did not decrease other physiologically important reactive oxygen/nitrogen species (ROS/RNS) (e.g., superoxide, nitric oxide, hydrogen peroxide) [8]. Fifteen years later, the research on H₂ gas has resulted in over 2000 publications on regarding its potential medical applications. Over 100 human studies show translational potential from animals to humans in a wide range of diseases. These include conditions such as metabolic syndrome [183,184], diabetes [185], hyperlipidemia [186], Parkinson’s disease [187], cognitive impairments [188], rheumatoid arthritis [189], chronic hepatitis B [190], vascular function [191], exercise performance [192,193], cerebral infarction [194], and others as reviewed previously [4,195]. In 2017, a clinical trial using inhalation of hydrogen gas was approved as an advanced medicine by the Ministry of Health, Labor, and Welfare of the Japanese for the treatment of post-cardiac arrest syndrome [196].

In 2019 the world was hit by a pandemic caused by the virus SARS-CoV-2, leading to a disease called COVID-19. Millions of people around the globe were affected. As of the end of February 2023, the World Health Organization (WHO) reported that there were 755,703,002 confirmed cases, and 6,836,825 deaths [<https://covid19.who.int/>] (accessed on 15 January 2023)]. Hydrogen treatment has been used in clinical trials for COVID-19, and used in hospitals in some regions, with positive effects [197,198].

8. Physicochemical Properties of Hydrogen

The molecular weight of hydrogen gas is the lowest of all molecules. It is hard to envisage how it would be recognized by a classical receptor mechanism, so there must be some other modes of action [199]. It will also not react with thiols in the classical way suggested for nitric oxide, H₂S, and other ROS. It has a very high kinetic diffusivity and has the highest effusion rate. This makes storage of hydrogen gas or hydrogen water very difficult. Hydrogen can easily permeate plastic containers, and can cause hydrogen embrittlement in metals [200]. At room temperature, solubilized hydrogen at 0.78 mM has a half-life of approximately 2 h depending on the volume of water and the exposed surface area [201]. H₂ will rapidly revert to the gas phase, meaning any enriched solution needs to be made and used fresh, which needs to be considered if used therapeutically or in agriculture [43].

9. Pharmacological Activities of Hydrogen

The pharmacological activities of hydrogen seem to be as diverse as there are numbers of conditions. Hydrogen modulates signal transduction, miRNA expression, protein phosphorylation cascades, and mitochondrial activity. However, the underlying molecular mechanisms and primary targets by which hydrogen exerts these pleiotropic biological effects remains elusive. Although some of the effects are thought to be mediated by the hydroxyl radical scavenging capacity of H₂, it is unlikely that all the effects are affected by this mechanism [195]. However, a recent study suggested that Fe–porphyrin, which is rich in mitochondria and erythrocytes, acts as a redox-related biosensor of H₂ [202]. It also catalyzes the reaction of H₂ with hydroxyl radicals, as well as with CO₂ molecules to produce the gasotransmitter carbon monoxide, which is known to have profound therapeutic effects [202,203]. Recent research also points to the benefits of molecular hydrogen on the functional state of erythrocytes in a model of simulated chronic heart failure. It was found that in rats, inhalation of 2% H₂ resulted in an increase in ATP and 2,3-bisphosphoglycerate, and consequently improved microcirculation and oxygen transport [204]. They also found that H₂ administration decreased lipid peroxidation and increased levels of catalase [204]. The upregulation of endogenous antioxidants by molecular hydrogen has been frequently reported [195]. Specifically, H₂ has been demonstrated to induce the translocation of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf-2) into the nucleus [205]. The activation of the Nrf2/keap1 pathway and the downstream induction of heme-1 oxygenase play important roles in the antioxidant activities of molecular hydrogen [206]. Several other properties and interactions have been mooted for how H₂ interacts with biological systems, including through its redox potential [199] or in a physical interaction which is akin to that of Xenon. Such mechanisms have recently been reviewed [207], but much more experimental work needs to be undertaken to support or confirm such actions of H₂.

10. Methods of Administration

There are several methods for hydrogen gas administration, including inhalation of H₂ gas [208], tube feeding of H₂-rich solution [209], intravenous injection of H₂-rich saline [210], H₂-rich dialysis solution for hemodialysis [211], hyperbaric H₂ chamber [172], bathing in H₂-rich water [212], increasing H₂ production by intestinal bacteria [213], topical application [214], oral ingestion of hydrogen-producing tablets [215], and simply drinking hydrogen-rich water (HRW) [183]. HRW can be prepared by bubbling H₂ gas into water under pressure, electrolysis of water ($2\text{H}_2\text{O} \rightarrow 2\text{H}_2 + \text{O}_2$), and by reaction with metallic magnesium ($\text{Mg} + 2\text{H}_2\text{O} \rightarrow \text{H}_2 + \text{Mg}(\text{OH})_2$) or other metals [195]. Several products from ready-to-drink beverages in aluminum pouches/cans [216] and electrolytic devices to H₂-producing tablets and inhalation machines are readily available to consumers. However, not all products may produce/contain concentrations of H₂ equivalent to or with the stability of those used in human studies [170].

11. Conclusions

Hydrogen as a medical therapy has been around for a very long time, often in situations where it was not realized that the presence of H₂ was the active agent. The history of the impact of H₂ on biological systems can probably be traced back to the writing of Hippocrates [132] and Herodotus with the concept of the Fountain of Youth [133]. However, the first evidence of experiments with H₂ and medicine probably stem from the late 18th century. Thomas Beddoes seemed to be determined to bring the use of gases to the medical world, with the instigation of the Medical Pneumatic Institution. He published about hydrogen in 1793, for example. Perhaps it was fortuitous that he employed the brilliant Humphry Davy, but his work at the institute brought nitrous oxide (N₂O) use to the forefront, despite it being known by Priestley previously, for example. Slightly before this, Tiberius Cavallo was working on respiration. Interestingly, both Cavallo and Davy used hydrogen, in what appears to be control experiments—or were they hoping hydrogen might be useful in its own right?

Regardless of the wide-ranging work, and very long papers by Cavallo and Davy, and indeed Beddoes [paper has been accepted, waiting for ref], very little traction was seen in the biological hydrogen world (the Medical Pneumatic Institution closed in 1802). H₂ gas was found to be useful for diving in the 1940s, but its wider medical effects were largely ignored. In 1975, Dole et al. [172] brought hydrogen back into the literature, but it was not until 2007 [8] that many researchers took much notice of H₂. Since then, it has been worked on by groups around the world and even used to aid people during the recent SARS-CoV-2 pandemic [197,198].

Despite the skepticism of people including David Jones in 1996, and the skepticism of the properties of spring waters and the pseudoscience surrounding its use, there is now a significant body of literature showing that H₂ has positive medical effects [195], potentially useful for neurodegenerative diseases, diabetes, and even in sports to enhance performance and for helping in sports-induced injury [193].

There has been a rich, and a rather on and off history of hydrogen in medicine, but now in the 21st century it is time for this often overlooked molecule to take a more central stage and be considered for wider medical use. Perhaps this time the interest in the medical effects of H₂ will not wane as it has through history.

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