

# Brief History of Oxygen

Subjects: [Chemistry](#), [Inorganic & Nuclear](#)

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Oxygen, a paramagnetic, diradical gaseous (at room temperature) molecule, is instrumental to life as we know it. It is also crucial to some medical therapies, used in multiple industries and has even been found on other planets.

The importance of oxygen cannot be overplayed.

ageing

exoplanets

hypoxia

Lavoisier

medical therapies

mitochondria

## 1. Atmospheric Oxygen and Its Evolution

Oxygen at the present time comprises approximately 21% of the Earth's atmosphere. Early atmospheric conditions were devoid of oxygen. Studies of ancient rock samples, for example, can give an indication of oxygen levels over history <sup>[1]</sup>. It is suggested that oxygen concentration rose in the atmosphere between 2.5 and 2.0 billion years ago. A study in 2000 <sup>[2]</sup> looked at the oxidation of sulfur and concluded that 2450 million years ago, the atmospheric oxygen was low as were the potential rates of oxidation.

The only source of atmospheric oxygen before photosynthesis was probably the photolysis of water, leading to hydrogen as a second product that would have been rapidly lost into space <sup>[3]</sup>. Furthermore, the oxygen would probably have been scavenged from the atmosphere by the reductive gases from volcanoes such as hydrogen. Therefore, for the first part of the Earth's history, the build up of oxygen in the atmosphere was not possible and indeed appeared to be depressed. Although it is thought that the generation of oxygen from photosynthesis started approximately 3.8 billion years ago, most of it would have been produced in the oceans and then it would have reacted with the minerals from the weathering and runoff from rocks, partly  $\text{Fe}^{2+}$  which left the iron deposits seen today. This process may have lasted as long as 2 million years. Eventually, photosynthetic  $\text{O}_2$  production would have out-competed the scavenging and atmospheric oxygen would rise <sup>[3]</sup>.

During the Permo–Carboniferous period, the atmospheric oxygen rose to approximately 35%, as opposed to the 21% seen today. This led to the growth of giant insects, and it was thought that wildfires were more common too. The appearance of large plants and the burying of large quantities of organic matter may have been the main cause for this oxygen concentration rise <sup>[4]</sup>. During the Mesozoic era, it was thought that the oxygen concentration dropped to approximately 15%. However, this has been disputed by some, who say that the record of wildfires indicates that the oxygen concentration was much higher, and they also conclude that no modelling will support the notion of such low atmospheric concentrations <sup>[5]</sup>. Of course, what researchers do know is that today the levels are around 21%.

Of course, today, maintenance of Earth's atmospheric oxygen is reliant on photosynthesis [6]. However, how stable is the oxygen concentration in the atmosphere? Looking at the atmospheric oxygen over the last 100 years and then projecting what might happen in the near future, it has been suggested that oxygen levels will drop from 20.946% to 20.825% [7]. This is caused by human activity—fossil fuel consumption, and authors say: “It is time to take actions to promote O<sub>2</sub> production and reduce O<sub>2</sub> consumption”. Others agree, and report that the future dissolved oxygen in the oceans over the next 100,000 years is likely to be severely depleted [8]. This is due to the fact of human activity. As the climate changes, the surface 500 m of the oceans will have less oxygen solubility, but there will be effects at greater depths. This is a sobering thought.

It should not be forgotten that molecular oxygen is not the only form that exists or is of interest. Ozone (O<sub>3</sub>) has been in the public awareness since it was reported that the atmospheric ozone layer was being depleted, for example see [9]. Ozone was extensively studied by Christian Friedrich Schönbein (1799–1868), but it was Jacques-Louis Soret (1827–1890) who determined its formula in 1865 [10][11].

Other forms of oxygen include singlet oxygen and the superoxide anion, the latter also known historically as hyperoxide. Singlet oxygen is an excited form of molecular oxygen (O<sub>2</sub>(a<sup>1</sup>Δ<sub>g</sub>)) and has been known for approximately ninety years [12]. Much of the work was carried out by Christopher S. Foote and his colleagues in the 1960s, but they were reassessing work already carried out approximately thirty years earlier [13]. Superoxide anions are molecular oxygen with an extra electron, but this has no pair in the outer shell, so that this is a free radical (O<sub>2</sub><sup>•-</sup>). Irwin Fridovich and H. Moustafa Hassan wrote about its toxic effects in 1979, and Pauling suggested that it was proposed through the work of quantum mechanics [14]. Lynch and Fridovich were also writing about the effects of superoxide on the membranes of erythrocytes in 1978 [15]. Superoxide readily dismutates to hydrogen peroxide, especially at low pH, and it is a reaction catalysed by superoxide dismutase (SOD), the latter being discovered by J.M. McCord and I. Fridovich in 1968 [16]. Once such oxygen-based compounds are generated, there is the potential for the production of further downstream oxygen-rich compounds collectively known as reactive oxygen species (ROS) and includes the hydroxyl radical (•OH). Their importance came to the fore with the realisation of the importance of the respiratory burst in white blood cells and the role of these compounds in host defence. The enzyme responsible was found in 1965 [17], known as the NADPH oxidase. Lack of this enzyme leads to the condition known as chronic granulomatous disease (CGD), where patients have a deficient immune response against pathogens and die young [18].

## 2. Discovery of Oxygen as Part of Metabolism and Ageing

Oxygen is instrumental for the metabolism of many organisms. Oxygen acts as the terminal electron acceptor in humans, for example, where four electrons are used to create water, which is then lost through the skin or breath. Without the removal of electrons by oxygen at the end of the electron transport chain, the mitochondria would be unable to create an electrochemical potential across the inner mitochondrial membrane. This potential was, of course, mooted by Peter Mitchell [19] (see also [20]). Lack of full reduction of oxygen leads to the production of oxygen-free radicals, notably, the superoxide oxide anion (O<sub>2</sub><sup>•-</sup>) [21]. Such radical production leads to a cascade of oxygen-based compounds, such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and the hydroxyl radical (•OH). Such ROS led to

the idea that their presence, and indeed over accumulation in cells, leads to the ageing process. This was suggested in 1954 [22][23] with papers reporting the presence of free radicals in biological systems [24]. One of the most prolific writers on the subject was Denham Harman (e.g., [25][26]). The idea still has traction today and is widely researched (e.g., [27]).

The idea of oxygen being involved in biological systems, of course, has a much longer history, spanning back to the work of people such as Lavoisier, as discussed above. Mitochondria were first described in the latter part of the 19th century by people such as Rudolf Albrecht von Kölliker (in 1857) and Richard Altmann (in 1898). Fletcher and Hopkins, in 1907, showed that oxygen caused the disappearance of lactate in stimulated muscles. Work by Meyerhof on oxygen and glycogen metabolism was published in 1927 [28], by the 1940s, the cellular location of some of the electron transport chain complexes was being unravelled [29], and by the 1960s the system was quite well characterised. For a good overview of the history of oxygen in metabolism see [30].

The lack of oxygen in biological systems is often referred to as hypoxia. This can be a somewhat misleading term. Atmospheric oxygen is 21%, as stated above, but not many cells in a body will be exposed to this concentration of oxygen. There are many conditions under which the oxygen tension accessible to cells is driven even lower, including during wounding and cancer, which would be true hypoxia. However, today the term hypoxia is widely used to mean an oxygen tension below 21% and not just in the case of true hypoxia. A history of its use was given by Richalet [31], who states:

“Viault and Jolyet used “Hypohématose” in 1894, but this term has not been used since. Hypoxybiosis first appeared in 1909 in Germany, then hypoxemia in 1923 in Austria, and hypoxia in 1938 in Holland. It was then exported to the United States where it appeared in 1940 in cardiology and anesthesiology. The clinical distinction between anoxia and hypoxia was clearly defined by Carl Wiggers in 1941. Hypoxia (decrease in oxygen), by essence variable in time and in localization in the body, in contrast with anoxia (absence of oxygen), ...”

How cells survive low oxygen, and recover from such conditions, is important to understand. Reperfusion injury, where oxygen is reintroduced to tissues and cells, can lead to damage partly through the generation of ROS [32]. The role of low-oxygen tension in cancer is also important to understand [33].

The use of oxygen in cells is not confined to respiration or causing damage. It has been recognised for many years that ROS and related compounds are instrumental in the control of cellular activities [34]. This was brought to a fore by the publication of the role of nitric oxide (NO) in cell signalling events in 1987 [35]. This opened the door to the idea that other similar molecules could be used for signalling including the superoxide anion, hydrogen peroxide, hydrogen sulfide and even hydrogen gas. It is interesting to note that the generation of NO by the enzyme nitric oxide synthase (NOS) is an oxygen-dependent reaction.

Therefore, the role of oxygen in biological systems has a long history, but is also immensely important to understand. Its role in respiration and cell signalling are vital for the correct functioning of the cell, but the absence

of oxygen is also important to consider, especially in tumours. Therefore, this segues into how oxygen can be used in medicine.

### 3. Oxygen and Its Uses in Medicine

Hyperbaric oxygen therapy (HBOT) <sup>[36]</sup> was probably first used in 1662 by Henshaw <sup>[37]</sup>. In 1789 Lavoisier and Seguin reported that high oxygen was detrimental to health, thus dissuading people from using it. This sentiment was probably exacerbated by Bert in 1878, who looked at oxygen toxicity in more detail. By 1887, the concept of HBOT was looked upon more favourably following work by Arntzenius <sup>[37]</sup>. Many hyperbaric chambers were built including examples in North America in 1860 and 1861. Edwards <sup>[37]</sup> states that Cunningham built a massive chamber in Cleveland that was “64 feet in diameter, was 5-stories tall and had 12 bedrooms on each floor”. In 1937, decompression sickness was successfully ameliorated using HBOT by Behnke and Shaw. According to Biggs et al. in 2022 <sup>[38]</sup>, there were 13 FDA approved uses of HBOT including treating “gas embolism, carbon monoxide poisoning, decompression sickness, and radiation necrosis”. They also state that there are some unusual uses too including “cancer, mild traumatic brain injury (mTBI), and Alzheimer’s disease”.

Oxygen is used too, of course, at normoxic concentration, especially for trauma or if a person has breathing difficulties. However, it has also been suggested that oxygen can be mixed with other gases, which may have a synergistic effect. An example of the this is the suggestion that oxy-hydrogen gas (a mixture of oxygen and hydrogen at a 1:2 ratio) can be used for the treatment of severe COVID-19, the present pandemic caused by the SARS-CoV-2 virus <sup>[39]</sup>.

### 4. Oxygen and Space

The study of oxygen is not confined to here on Earth. In 2013, the Hubble Space Telescope reported evidence of oxygen at the exoplanet HD 189733b <sup>[40]</sup>. It is also proposed that the James Webb Space Telescope will be able to detect oxygen on similar planets <sup>[41]</sup>. Tian suggested <sup>[42]</sup> that the creation of what is referred to as a massive oxygen atmosphere is not inevitable and that there might be a bimodal distribution of such exoplanets. There is the inevitable excitement that if oxygen can be found on other planets that such places may harbour life <sup>[43][44]</sup>.

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