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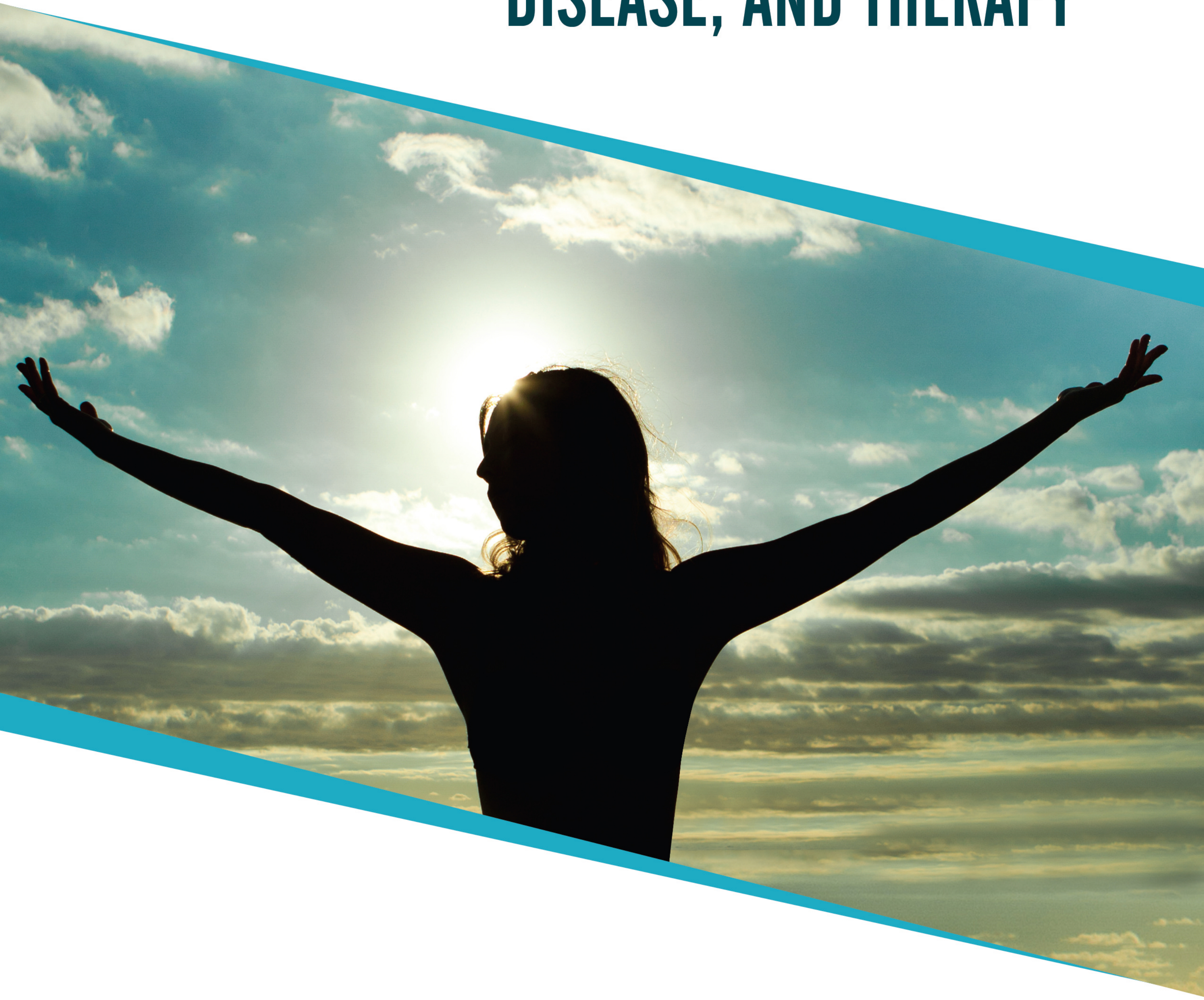
OXYGEN, THE BREATH OF LIFE: BOON AND BANE IN HUMAN HEALTH, DISEASE, AND THERAPY



Olen R. Brown

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Oxygen, the Breath of Life: Boon and Bane in Human Health, Disease, and Therapy

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CONTENTS

FOREWORD

We are constantly barraged with scientific publications and news media regarding issues pertaining to our health in regard to prevention and cures, product defects, food benefits and dangers, renewable energy, fossil fuels, global warming, climate change, and other concerns. The contradictions and reversals in opinions on many of these subjects make us question where the truth lies. This book is an unbiased overview and synopsis of the benefits and detriments of oxygen culminating from more than 56 years of theoretical and laboratory research by the author.

As delineated in the title of this book, the effects of oxygen in its multiple forms and compounds can be a benefit or detriment to our way of life especially to our health and to the world as we know it. These are important but very complex topics. In fact, even though the oxygen element was isolated and discovered in or around 1774 it will be obvious after reading this book that our understanding of the influence of this element has made great strides but in reality, we have only uncovered the tip of the iceberg for what lies before us in the future.

Mastering a subject or concept throughout decades of one's professional career is one thing but taking the time and then having the patience and ability to assimilate and record the obtained wisdom and experience in a clear and concise document that contains details that can be read and understood by an outsider to the particular field is a totally different matter. This book provides such readily understandable sections for readers who are looking for information to initiate research on a particular issue that may be related to or affected by oxygen. But, just as important, the book also contains historical facts, theoretical and experimental scientific data, and detailed explanations with illustrations for a reader more experienced with chemistry, physics and/or biology who is seeking an in depth understanding in order to formulate his or her own opinions and conclusions regarding the benefits, detriments, and/or dangers associated with oxygen as related to a specific topic of interest.

For myself as one with a limited background in chemistry and biology obtained from college level freshman courses, it was refreshing to read an unbiased informative comprehensive treatise on what the scientific and medical communities have learned about oxygen up to this time in history. I believe anyone seeking knowledge on any of the many topics associated with oxygen will agree that this is a very comprehensive and well written book. So, read, enjoy, and become informed.

David Hullender

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PREFACE

The facts of science are published daily in a bewildering flurry of information that arrives in scientific papers and is immediately summarized (often incorrectly) by the press and on the internet. This book was written with a broader view: to try to make sense of what we know, or think we know, and from my desire to understand and explain things. As a scientist through most of six decades, it has been a great pleasure to teach students at all college levels and my interests include microbiology, biochemistry, molecular biology, toxicology, and the history of science.

The specific focus of my research is oxygen and its role in health and disease. This includes oxygen free radicals, cellular defenses against the toxicity of oxygen, and the central role of oxygen in cellular metabolism. Oxygen's dual nature was referred to as oxygen's boon and bane by a colleague, Irwin Fridovich, and I have chosen these apt words in the title of this book. Contributions from my laboratory include: evidence that specific enzymes, but not enzymes in general, are sites of oxygen toxicity, and with Richard Seither, while a student, the discovery that hyperoxia induces genetic stringency in microbes. Stringency stops grown and metabolism and protects cells from damage.

I began laboratory research in the 1960s, an exciting time for scientists because of NASA and the stated objective by President John F. Kennedy to "Go to the moon and do it in this decade". The US Space Program chose pure oxygen at low pressure for manned space flight. The Russian Space Program used larger rockets and chose a two-gas system of nitrogen and oxygen at atmospheric pressure because of the toxicity and fire hazard of pure oxygen. NASA's choice ultimately led to a tragic fire on the ground in a test capsule filled with low-pressure, pure oxygen and caused the death of three Apollo 1 astronauts in 1967. My research on the mechanisms of oxygen toxicity was relevant to NASA's Space Program and also to the Office of Naval Research where the toxicity of oxygen was a concern for deep sea diving.

This eBook was written to bring together in a popular science version, while remaining true to science, the many and varied aspects of oxygen, without which we cannot live for more than a few minutes, but which is lethal at concentration only a few times that found in the ordinary air we breathe.

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Scientific study, experimentation, and discovery brought together many individuals in my laboratory and interactions with students; and generous and helpful colleagues contributed to and helped me prepare to write this eBook. I thank them all with a gratitude borne out of being fellow travelers in science and discovery. One of the great joys in science for me has been the attempt to understand our world in the broadest sense that is reasonably possible. Science is about asking the "how" questions. Answers are found in individual science publications and other writings by scientists in fields from astronomy to xenobiotics (chemicals, foreign to nature). In my lectures and study to understand science and especially in writing this book, I have freely drawn on this body of work by many scientists from many fields and obviously I make no claim of originality except for the research I have published.

I thank many talented individuals who created the images I have chosen to use from those made available on the internet licensed as "free to modify, share, and use commercially", and those who generously provided other images I have acknowledged in figure legends.

I thank Cameron Brown for his assistance, especially for his computer skills with manuscript preparation, and John Allen and Emily Brown, especially for their critical reading for content and clarity, of this e-book.

CONFLICT OF INTEREST

The author confirms that author has no conflict of interest to declare for this publication.

DEDICATION

To my former students and research associates.

CHAPTER 1

Oxygen: Origin in the Universe and Brief Chemistry

Abstract: Oxygen is the 3rd most abundant element in the known universe. Only hydrogen and helium, in that order, are more abundant. The big bang theory of creation asserts that all the elemental oxygen on earth was created late in the life of a dying star. On earth, oxygen is the most abundant element in the lithosphere (land), hydrosphere (water), and atmosphere (air). More precisely, the lithosphere is all the crust or solid, upper portions of the Earth; the hydrosphere includes all the rivers, lakes, seas, and oceans; and the atmosphere is the gas-filled space above and near the earth. Atomic oxygen is chemically and biologically reactive and primarily exists as molecular oxygen (O_2, two like atoms combined), or in combination with certain elements (primarily metals). Oxygen forms reactive intermediates and free radicals including peroxide, superoxide and hydroxyl radical. The latter is said to be the most reactive species known in chemistry. Oxygen has a unique arrangement of electrons that is conducive to one-electron transfer reactions that can produce oxygen free radicals and cause biological oxidant stress. However, oxygen is especially suited to serve as the terminal acceptor of electrons in the biological process of electron transfer that is linked *via* coupled reactions to oxidative phosphorylation that creates adenosine triphosphate (ATP), the universal storage and transfer form of energy for all aerobic life on earth.

Keywords: Atmosphere, Aufbau order, Big bang, Burning, Christ's last breath, Combustion, Dmitri Mendeleev, Double bond, Elemental oxygen, Final electron-acceptor, Free radicals, Hydrogen peroxide, Hydrosphere, Hydroxyl radical, Inflation, Lithosphere, Nucleosynthesis, Ozone, Periodic table, Photosynthesis, Sir Fred Hoyle, Superoxide dismutase, William A. Fowler.

Olen R. Brown

INTRODUCTION

Oxygen is like Goldilocks' porridge, chair and bed in the children's story *The Three Bears*: oxygen is "just right"; just right for life.

By analogy with Goldilocks' porridge (neither too hot nor too cold), oxygen for living systems is neither too reactive nor to inert; its chemical and biological reactivity is just right. Oxygen has many roles in cells. It must oxidize (burn in a controlled way) the food in our bodies to release energy in a manner that does not consume us. Energy must be stored in a transferable, accessible form and adenosine triphosphate (ATP) performs this function uniquely for growth, repair, moving, and thinking. ATP's stored energy, made possible by biological reactions involving oxygen, is just right. It is somewhat like the dynamite discovered by Alfred Nobel that so tamed the energy of gunpowder that it literally could move mountains but was safe enough for untrained men to handle because it required a lighted fuse to detonate. Oxygen has just the "right stuff" to snatch electrons from chemicals like the sugar glucose. Glucose is derived metabolically in cells by enzymes and is made abundantly by plants with energy ultimately derived from the light of the Sun, a nuclear furnace that is just the right distance away to be safe (93 million miles). Thus, it is a property of electrons of oxygen (mystically having both particle and wave-like properties) that undergirds an exquisite system that efficiently stores energy in ATP that is transported for use everywhere in our bodies.

By further analogy with Goldilocks' chair and bed (just the right size for sitting and softness for sleeping), oxygen is correct in size and electronic structure to readily diffuse into cells and fit energetically into complex metabolic schemes as substrate, intermediate, and product that are easily inspired, reacted, and excreted. A gaseous element, it can freely diffuse in the atmosphere where it maintains a near constant concentration of approximately 21%. It can diffuse from air in the lungs into red blood cells, requiring only hemoglobin and a few regulatory molecules to serve as subway trains and ticket conductors. Oxygen thus has free entry into cells and it requires no special passport to cross their membrane borders, partly because of its small size. Once inside cells, oxygen freely diffuses around the cytoplasm and into organelles called mitochondria. Mitochondria work like factories to make ATP, which functions like charged batteries to do work everywhere in the cell. Oxygen participates in biosynthesis and in oxidation-reduction reactions and combines with carbon to form carbon dioxide that is readily excreted at low cost in energy. To paraphrase Descartes: “I have ATP, therefore I am”.

Each molecule of atmospheric oxygen has two atoms of oxygen. Oxygen forms various structural components in cells and important metabolic intermediates with many different functions and many different oxygen contents. For example, each molecule of ATP has 13 atoms of oxygen. Whenever oxygen burns an organic substance, whether in a forest fire, a log in your fireplace, or in the mitochondria within cells of your body, the process is vastly different, but the primary end products are simple molecules of water and carbon dioxide. They are non-toxic (safe) wastes and are easily disposed of by diffusion out of cells and into the lungs where they are exhaled with minimal expenditure of energy. Water, by mass, is approximately 89% oxygen; carbon dioxide is approximately 73% oxygen; and the entire human body is approximately 65% oxygen. This near universal presence of oxygen throughout the biochemistry of cells is further, strong evidence for the essential nature of oxygen for life. In the form of water, oxygen is considered almost universally to be the signature of life by searchers who hope to discover life on other planets. To further paraphrase Descartes: “I have oxygen, therefore I am”.

OXYGEN IN THE UNIVERSE

To continue our journey toward an understanding of the role of oxygen in Nature, it will be helpful to start at the beginning, or what many scientists now believe to be the beginning.[1] The dominant, current theory in astrophysics about the origin of the universe is the “big bang”. The term big bang was coined by Sir Fred Hoyle [1] as a perhaps derisive term (he later denied it was meant to be derisive) for the event that is generally claimed in science to be the origin of the Universe.[2] An origin for the Universe implies an Originator and some preferred the idea that the Universe had always existed.

Hoyle, about 70 years ago, disagreed with the theory that the universe had a

CHAPTER 2

Oxygen: Essential Role in Life

Abstract: Oxygen is especially suited to serve as the terminal acceptor of electrons in the biological process within mitochondria of electron transfer. This process is linked *via* coupled reactions to oxidative phosphorylation that creates adenosine triphosphate (ATP), the universal storage and transfer form of energy for all aerobic life on earth. However, the unique arrangement of oxygen's electrons is conducive to one-electron transfer reactions that can produce oxygen free radicals and cause biological oxidant stress. Hans Krebs was the genius who uncovered the complex, biological cycle that we know as the Krebs cycle which revealed the long-hidden secrets of how the energy of consumed food is made available for cellular functions. Oxygen is the only element with the special combination of unique attributes required for cellular bioenergetics, the process of "cold" burning of food molecules to power the cell's energy needs. A special example of oxygen's role in "cold burning" is the firefly's luminescence.

Keywords: Apollo 13, ATP synthesis, Cellular respiration, Citric acid cycle, Coupled reactions, Cytochromes, Essential oxygen, Final electron-acceptor, Free radicals, Futile cycles, Hydrogen peroxide, Hydrosphere, Hydroxyl radical, Krebs cycle, Luciferase, Luciferin, Mitochondrial membranes, Oxidative metabolism, Ozone, Photosynthesis, Two-electron transfer, Valence electron.

INTRODUCTION

Oxygen has unique features, some of which are described in Chapter 1. As a molecule (diatomic oxygen) and as an element (monatomic oxygen) it is capable of undergoing reactions unique to living cells. Metabolism of cells is conveniently thought of in two categories: catabolism and anabolism. Catabolism refers to processes that break down chemicals to serve as nutrients for cells. Anabolism refers to the processes that create more complex molecules from simpler molecules. Growth, multiplication and repair of cells would not be possible

Olen R. Brown

without anabolism, and anabolism requires coupled reaction (subsequently to be described) to provide the necessary energy to create new bonds between atoms and parts of molecules.

Catabolism is a complex process involving many stages and many different organelles inside cells. Of interest to us here, is the fact that oxygen serves as the terminal receptors for hydrogen ions and electrons that are derived from chemicals like glucose. To better explain this process it is useful to consider how glucose brings energy into a process that occurs primarily in special organelles called mitochondria (singular mitochondrion). Organelles are intracellular structures that are bounded by membranes and designed for specific functions. With the exception of certain anaerobes, life as we know it on earth cannot exist without oxygen. This derives primarily from the fact that oxygen serves as the terminal acceptor of electrons in a long sequence of reactions whereby energy is transferred and eventually "stored" in adenosine triphosphate (ATP). It is this ATP that serves as the source of energy for life processes. Lawrence Krauss has written about this [1][1]. Respiration adds oxygen to the process as the terminal receptor of hydrogen ions and electrons removed from intermediates derived from sugar and taken through the cytochromes system where energy gets stored in ATP.

It is possible to roughly estimate the amount of oxygen consumed annually by Earth's human population. Of course, this requires assumptions and the estimate's accuracy depends on the validity of the assumptions[2]. There are data from various sources that differ. I shall make a few estimates and leave detailed calculation and evaluation to Chapter 4. A reasonable approximation of the quantity of oxygen consumed annually by the world's human population is 1.4 petagrams (a petagram is 10^{15} grams). Oxygen is produced by photosynthesis which generates one molecule of oxygen for each molecule of carbon dioxide. Photosynthesis is reported to produce approximately 550 to 642 petagrams (average = 596) of carbon dioxide annually [2]. Thus, the mass of molecular oxygen produced is 32/44 times 596 petagrams = 433 petagrams (calculated based on the molecular masses of oxygen and carbon dioxide, 32 and 44 grams). I estimate that humans use is about 1.4/433 which is 0.0032 (0.32%; approximately 1 out of every 300). Consider that most life forms on earth consume oxygen. This includes all the other land mammals, the fish and crustaceans, the arthropods, the insects, the aerobic bacteria; algae, and the plants themselves. The oxygen concentration appears to be remaining approximately steady in today's atmosphere. Humans are only a fraction of the total world's biota that consume oxygen. Is this calculation wrong that 1 of every 300 molecules of oxygen is used by human respiration? Could the data about atmospheric oxygen and carbon dioxide concentrations be incorrect? Are we missing something here that is important to our conclusions about the global balance of carbon dioxide and oxygen? I will address this important issue again in Chapter 4.

CELLULAR RESPIRATION

Cellular respiration is the process of oxidative phosphorylation within cells which results in formation of ATP. There is the intake of oxygen and the release of carbon dioxide. This is such a broad subject that I must limit content, and I shall focus on outlining biological processes at the cell level that are helpful in providing an understanding of the specific role of oxygen.

Consider a molecule of oxygen that has arrived at a typical cell. (In Chapter 8 oxygen transport is described, including the intricate mechanisms for "loading" of oxygen on red blood cells in the lungs and "unloading" at the cellular site). Oxygen is less soluble in water as temperature increases and the amount that can dissolve in blood plasma that bathes cells is relatively low at the partial pressures of oxygen normally experienced when breathing air. Calculations show that there are about 3 ml of oxygen per liter of blood at the partial pressure of 100 mmHg which approximates the concentration near to but outside of cells that are well-oxygenated. There are about 5 liters of blood in the average person and a total of approximately only 15 ml of oxygen dissolved in blood plasma; far too little to supply the needs of the body and explanations are in order (see Chapter 8).

There are no special means (such as binding to membrane proteins) for oxygen and it gets inside cells by simple diffusion which is temperature-and concentration-dependent (oxygen moves from higher to lower concentration). Oxygen can move through interstices in the lipid bi-layer of the membrane or through plasma filled channels in membranes. Thus, a never-ending supply of

CHAPTER 3

Discovery and History of Oxygen

Abstract: Oxygen was first isolated by Carl Scheele, officially discovered by Joseph Priestly (because he published first), and named by Antoine Lavoisier. Air had historically been known to be required for both animal respiration and for combustion. With the careful laboratory work of Lavoisier, involving weighing and measuring, air was discovered to not be a single element but was found to be composed primarily of two gases, one of which was oxygen in the proportion of about 20%. Priestley published that in a sealed chamber this "pure form of air" (later named oxygen by Lavoisier), was what kept the mouse alive in his experiment. The work of Priestley and Lavoisier disproved and overthrew the Phlogiston Theory which speculated that a substance "phlogiston" was present in air which after combustion became dephlogisticated. The discovery of oxygen as an element and its roles in animal respiration and in combustion, were seminal events in the period of the late 1700s when chemistry transitioned from a largely "black art" (alchemy) to science. Thus, in addition to being essential to life (certain bacteria are exceptions), oxygen had a significant role in the development of modern chemistry.

Keywords: Air, Albert Szent-Gyorgyi, Benjamin Franklin, Bomb calorimeter, Burning, Calorie, Carbon dioxide, Carbonation, Combustion, Dephlogisticated air, Father of chemistry, Guinea pig experiment, Isolation-purification, Lavoisier, Linus Pauling, Marie-Anne Pierrette Paulze, Mouse experiment, Oxidation, Oxygen, Phlogiston, Priestley, Pure oxygen, Rubber eraser, Scheele, Scurvy, Second Law, Unitarian minister, Vitamin C.

DISCOVERY OF OXYGEN

Introduction

It is commonly written by historians of science [1, 2] that oxygen was first isolated (separated from air) by Carl Scheele (1742-1786), officially was disco-

Olen R. Brown

vered by Joseph Priestley (1733-1804) and was named by Antoine Lavoisier (1743-1794). However, the history of the discovery of oxygen is controversial because of how and when these scientists made their discoveries and when they published their results. There is evidence that Scheele was somewhat introverted, was very meticulous, delayed to report, and never aggressively sought credit during his lifetime. The evidence is, however, clear that Scheele was the first to isolate oxygen and this occurred in 1771-1772, but he did not publish until 1777 in his *Treatise on Fire and Air.* Priestley, however, published his work dealing with the isolation and some experiments with the gas in 1774.

The research by these men, especially Priestley, was foundational for setting precedents for chemical research that involved meticulous record keeping and careful observation. A confusing and incorrect theory of gases, called the phlogiston theory, dominated chemistry in the 1770s [3]. Phlogiston was incorrectly thought of as the "stuff" that was released from burning of a substance. More specifically, the phlogiston theory was an ancient idea that a "fire-like" substance called phlogiston was present in all combustible substances, and was released by combustion. Georg Ernst Stahl (1660-1735) is usually credited as the chief proponent and developer of the phlogiston theory which dominated Chemistry in Europe during his scientific lifetime and up until near the end of the 18th Century [4]. A primary proponent was Joachim Becher (1635-1682) who was a German chemist, physician and adventurer who thought that matter was made of three "earths": the vitrifiable, the mercurial, and the combustible. He experimented with changing sand from the Danube into gold and his extraordinary claims (which apparently were believed by some, at least for a time) led to his disgrace and more strikingly, forced him to flee [5].

The phlogiston theory was an unsuccessful attempt to explain combustion and rusting of metals (we now call the latter oxidation and know oxygen is involved). The phlogiston theory was overturned largely because of the work of Lavoisier (subsequently to be detailed in this chapter) that greatly advanced chemistry by proving that combustion required oxygen. This Lavoisier documented by carefully weighing the masses of substances before and products after reaction in closed containers. This proof of the role of oxygen in combustion solved a mystery and overthrew a complicated and ugly theory but also contributed greatly to what became known as "the chemical revolution" that stirred the scientific world beginning near the end of the eighteenth century.

Oxygen is a small, diatomic molecule. A classic, but now little used, depiction of diatomic oxygen shows the inter-lapping of the orbitals of shared electrons that create the double bond between atoms (Fig. **1**). Two atoms of oxygen are shown each with their outer orbitals completed by 8 electrons with 2 shared. The double bond results in four electrons that can be removed, one at a time, and this has consequences that will be later discussed. Oxygen is a colorless gas at ordinary temperatures near the earth's surface. It becomes liquid at -182.96 °C, and is referred to as Lox. Oxygen freezes at -361.82 degrees, and it has a very large expansion ratio at ordinary pressure and temperatures; therefore it can be compressed as a good storage form of breathable oxygen.

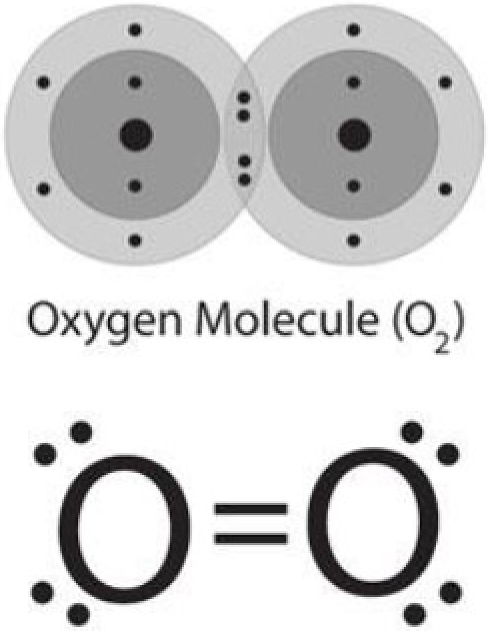

Fig. (1). Classical representation of diatomic oxygen.

Joseph Priestley

A thorough and authoritative account of Priestley's life, research and discoveries concerning oxygen was assembled by Carmen Giuta of LeMonde College [6].

CHAPTER 4

Oxygen Generation by Photosynthesis

Abstract: Evidence supports that all of the molecular oxygen present in Earth's atmosphere today could have been produced in the last 2,000 years. Photosynthesis by green plants, algae and related phytoplankton are the source of this atmospheric molecular oxygen. Green plants are the "sugar factories of the world" and have intricate microscopic systems within leaves that use sunlight, water, and carbon dioxide to produce carbohydrates and oxygen. Capture of photons from sunlight requires a complex array of pigments that include the green molecule chlorophyll. The photons are captured *via* absorption by pigments that are organized sequentially in a specific order within leaf structures called chloroplasts. Leaves have a complex, organized macroscopic structure and an even more complex microscopic structure. This organization begins with the shape and structure of the leaf itself. Leaves have an aerodynamic shape that allows them to survive in wind and rain and are oriented to capture sunlight. They have an outer waxy coating which retards water loss but with provisions (stomata) that regulate entrance and efflux of carbon dioxide, oxygen, and water vapor. The biosynthesis of carbohydrate from carbon dioxide requires energy input, and the leaf has intricate mechanisms for capturing sunlight to make chemical bonds in ATP. Great political turmoil recently has arisen over claims that carbon dioxide in the atmosphere is the determining factor in increasing the global temperature by amplifying the "greenhouse" effect. Based on speculation and questionable computer models, man-made (anthropogenic) carbon dioxide is said to be the cause of what initially was called "global warming", but more recently has been changed to "climate change". The ability to scientifically measure photosynthesis globally has become relevant for making intelligent decisions about climate change and atmospheric CO_2 concentration. There is reason to believe that natural (and/or future artificial) photosynthesis can maintain the balance of atmospheric $CO_{2.}$

Keywords: Aerobic life, Algae, Antennae, ATP, C3 plants, C4 plants, Calvin Cycle, CAM plants, Carbon dioxide, Chlorophyll, Climate change, Desert plant,

Olen R. Brown

Enzyme, Leaf, Lysozyme, Melvin Calvin, Oxygen, Peroxisomes, Petagram, Photosynthesis, Photosystem I, Photosystem II, Phytoplankton, RuBisCO, Stomata, Sunlight, Thylakoid membrane, Transpiration, Water vapor.

BIOLOGICAL PRODUCTION OF OXYGEN

Introduction and Overview

Molecular oxygen is significantly reactive even though this reactivity is reduced by the arrangement of its valence electrons as addressed in Chapter 2. Were it not for the production of oxygen by photosynthesis (of green plants, algae, and phytoplankton) essentially all of the oxygen on Earth would now be combined with other elements and likely only traces would be present in air. Thus, life as we know it would not exist on Earth. Photosynthesis also provides an important "sink" that captures CO_2 by "fixing" it into the complex carbohydrates of life.

The examination of photosynthesis in this Chapter, even though focused and limited in scope, will be designed to provide the basic information necessary for understanding two processes: oxygen generation and carbon dioxide removal with fixation into carbohydrates by green plants. Oxygen, the breath of life, is liberated by green plants (that also use oxygen for their metabolic respiration) and carbon dioxide (a simple form of carbon, somewhere between inorganic and organic carbon) is fixed fully into organic carbon. The carbon is initially fixed into a three-carbon sugar phosphate and eventually into sucrose that serves as a starting material for structural and energy requirements for the plants which then support animal life. A point that may be under-appreciated is the fact that both oxygen and carbon dioxide are gases and their presence in air makes them available as starting materials and products that readily enter and exit cells. Oxygen and carbon dioxide are present in air at nearly constant concentrations of approximately 21% and 0.04% (on a volume basis) in Earth's atmosphere today. Thus, the ratio of oxygen to carbon dioxide is approximately 500-to-1. Biological systems that capture and release these gases are efficient over this large range, and in photosynthesis 1 molecule of carbon dioxide is taken up for each 1 molecule of oxygen released.

I shall describe these complex photosynthetic systems in what may appear to be considerable detail. However, these descriptions are only an outline of the complexity present at ever deeper levels within plant cells. Photosynthesis efficiently manages the recycling of these two gases that have such different abundances with exquisite balance. Indeed, later in this chapter we shall explore how the large enzyme (RuBisCO) of the Calvin Cycle is able to catalyze two competing reactions involving carbon dioxide and oxygen as substrates [1]. Carboxylation of a substrate, common to both enzyme actions, results in carbon assimilation in one case and a competing reaction that reduces photosynthetic efficiency in the other case. Indeed, RuBisCO binds carbon dioxide stronger than oxygen and a region of the enzyme structure is a temporary reservoir for CO_2.

The energy that drives photosynthesis comes from photons of light delivered from the sun over approximately 93 million miles of cold, nearly empty space– about the right distance to render a nuclear fusion reactor safe for life. To use these photons, plants have unique antennae as part of an exquisite system that guides and delivers the energy so that it can be fixed in the bonds of biosynthesized organic molecules within the leaf. Recent studies using bacteria by researchers at Lawrence Berkeley National Laboratory and UC Berkeley [2] revealed that the mechanism of this biological energy-capture requires utilization of quantum mechanics for photosynthesis in certain bacteria (and probably in all systems). They found evidence of "quantum entanglements" that persist over picoseconds in this complex biological system, helping to account for its efficiency. If particles, such as two electrons in this case, are "entangled" any change in one is instantly reflected in the other. Their results were interpreted to indicate that photons exhibit this property in the bacterial light-harvesting complex. They suggested that this has implications for future attempts to design quantum-based technologies for computing. It is currently being used to create hybrid photosynthetic machines.

Thus, carbon dioxide, a single atom of carbon oxidized by two atoms of oxygen from the atmosphere where it is present at a concentration only two thousands that of oxygen, *via* the miracle of photosynthesis, creates the carbon backbone underpinning life on earth.

CHAPTER 5

Oxygen, Vital Element in Water

Abstract: Water is the most abundant molecule in which atomic oxygen is found on earth. Water is composed of two atoms of hydrogen (the simplest of the elements) and one atom of oxygen covalently bonded (four valence electrons are shared). Water covers about 71% of the land mass on earth and by weight water is approximately 0.33% of the atmosphere. It is the only element that is present in the earth-like temperature range as liquid, solid and gas. There is an earth-water cycle, and it nourishes, cleans and sustains the land with transpiration to clouds and condensation as rain, snow, sleet and hail. Our bodies vary in oxygen content, but the average is around 50%; slightly less in women than in men, and more in the skinny than in the obese. Oxygen has physical and chemical properties that are unusual and not predicted, compared to other small, simple compounds. It has maximum density at about 4 degrees Centigrade which causes lakes and ponds to freeze from the top down with interesting consequences. It is a good solvent for many chemicals and it forms the milieu of the cells of our bodies. It forms hydrogen bonds with itself which introduces unexpected structure in collected water molecules. Without it, life as we know it (and what other kind of life might there be?) would not be possible– we even search for it in space and on other worlds as a sign there might be life there.

Keywords: Atmosphere, Aquifer, Boiling point, Covalent bond, Diatomic, Dipole, Freezing point, Heat of vaporization, Hydrogen bond, Hydrophilic, Hydrophobic, Ocean, pH, Sea, Surface tension, Thales, Transpiration, Universal solvent, Water, Water cycle.

INTRODUCTION

Water covers approximately 71% of the earth's surface [1] and only 2.5% of this is fresh water and most of that is in ice with less than 0.3% in rivers, lakes and the

Olen R. Brown

atmosphere [2]. Amazingly, according to published data [2], only 0.003% of earth’s fresh water is found in “biological bodies and manufactured products”. It is the only natural substance that exists in all three states: solid, liquid, and gas at the usual temperatures and pressures found on earth’s surface [3]. Most scientists agree that without water life cannot exist.

Water is a small molecule, composed of two atoms of hydrogen and one atom of oxygen with shared electrons forming the oxygen to hydrogen bonds. Two valence electrons come from the two hydrogen atoms, and six valence electrons come from the one oxygen filling the orbital with eight electrons. The mass of water is 18 grams per molecule, and water is approximately 89% oxygen by mass. Water has a number of unusual physical properties. Compared to common liquids, water has the highest: surface tension, heat conductance, heat capacity, and latent heats of fusion and vaporization. High surface tension dictates size of drops in rainfall and controls biological properties within cells. Also, small bugs take advantage of this and some can walk and skate on water. Surface tension pulls water together when it is in small droplets (water is attracted to itself and tends to form a ball shape). In a small tube, water will form a meniscus which rises up the sides of the tube, and the meniscus is elevated higher in proportion to the smallness of the tube. Water will rise in the vasculature (small tubes) of plants, and will rise to the top of even tall trees, due to these forces plus the osmotic forces in the roots and transpiration in leaves that overcome the pull of gravity. This unexpected behavior of water results also from the propensity of water molecules to stick together and to stick to other surfaces. The latent heats of fusion and vaporization work to modulate heat near the earth’s surface, and the heat of vaporization is in control of the regulation of transfer of heat between ocean, seas, and the atmosphere.

WATER, A SMALL BUT UNUSUAL MOLECULE

Thus, water is a small, simple molecule but it has unusual and unexpected properties. One atom of oxygen and each of two atoms of hydrogen are held together by coordinate, but unequal, sharing of electrons (Fig. **1**). The valence (bonding) electrons are held more tightly (closely) to the oxygen atom which creates a slightly negative charge on one “side” of the molecule. The opposite occurs in the region around the two hydrogen atoms which are slightly and positively charged. Thus, the molecule is a dipole. The hydrogen atoms of the water molecule bond at an internal angle of close to 105 degrees and the water molecule looks something like Mickey mouse's head (Fig. **1**).

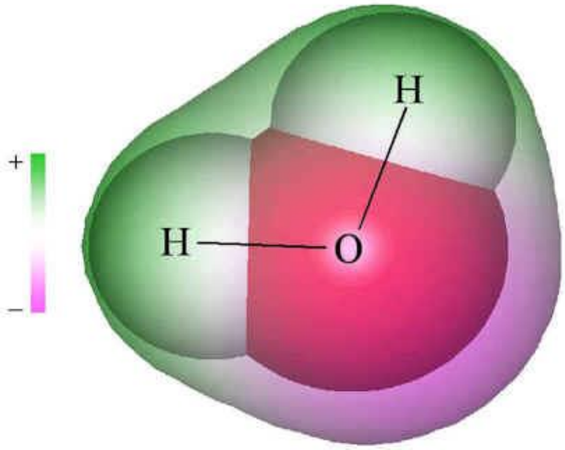

Fig. (1). Space-filling model of oxygen; one atom of oxygen (red) with two atoms of hydrogen attached by covalent bonds at an angle of 105 degrees, resulting in concentration of positive charge on one side and negative on the other.

In a collection of water molecules, there also is considerable orientation and organization of individual molecules. This results because water can form 4 intermolecular hydrogen bonds– an unusual number of such bonds for such a small, simple molecule (Fig. **2**). Although the hydrogen bonding is comparatively weak (only about 0.1 as strong as the typical covalent bond between atoms in a molecule) it is responsible for most of the unusual properties of water including: high freezing and boiling points, high heat capacity, high heats of fusion and evaporation, high surface tension, bipolar nature, and great ability to be a solvent for many chemicals. The high surface tension of water, as just discussed, causes it to rise in capillaries including the vascular systems of plants, even tall trees [4]. If water did not have (for its size and simplicity) the unusual, complex extremes in these physical characteristics, it could not function as it does in myriad ways, both inside cells and in nature's water cycle to clean, feed and restore the earth.

CHAPTER 6

Oxygen Therapy, The Early Years

Abstract: Since the discovery of oxygen, there have been swings from emphasis on the essential, beneficial nature of oxygen to focus on its damaging effects. Outright speculations and critically-considered hypotheses have ebbed and waned for the therapeutic use of elevated oxygen and practical applications of gas mixtures for deep-sea diving and pressurized caissons for construction under water. Oxygen as therapy has been proposed as beneficial or even a panacea. In some hands it was harmful and even deadly. The use of elevated oxygen tensions (as compressed air) began even before oxygen was isolated and identified from air. Oxygen was used as therapy and compressed air was extensively breathed by miners and workers in caissons tunneling under water to construct bridges. These practical, non-therapeutic applications of various breathing mixtures containing oxygen also contributed to scientific understanding of the physiology of oxygen in the human body. Elevated oxygen tensions also were used for U.S. Navy diving operations and laboratory experiments with humans and a variety of life forms. In the early years oxygen therapy was used for a wide variety of diseases, many of which were treated without any established connection to a mechanism of action. Thus, the therapeutic use, laboratory experimentation with, and practical applications of compressed air, gas mixtures at and below one atmosphere pressure, and hyperbaric oxygen has had an interesting, long, and colorful development that included charlatans (probably), adventuresome physicians ahead of their times, visionaries, and practical men of industry.

Keywords: Air embolism, Albert Behnke, Atmospheric pressure, Caisson, Carbon monoxide poisoning, CNS toxicity, Compound oxygen, Cunningham, Decompression sickness, Domicilium, Gas gangrene, Henshaw, Hyperbaric pressure, John Bean, John Haldane, Lorrain Smith effect, Paracelsus, Paul Bert effect, Pulmonary toxicity, Spanish flu treatment, USS Squalus.

Olen R. Brown

INTRODUCTION

In Chapter 2, the conclusions of Priestley, who is credited with discovering oxygen, were quoted to emphasize that from that early time forward, the hope that increased oxygen could be therapeutic was constrained by the caution that it could be harmful. After oxygen was available in purified form, and based only on preliminary medical experiments, oxygen unfortunately was elevated by some to the status of a panacea. An extreme example of oxygen therapy was a large iron sphere constructed to house patients in an atmosphere containing an elevated concentration of oxygen as therapy for various conditions. The therapy fell into disrepute and the sphere was razed for its iron content prior to WWII. The necessity to provide breathable atmospheres for: undersea operations (hard-hat diving suits, scuba gear, submarines, and caissons to support construction workers building bridge foundations under water); therapeutic uses; aircraft operating at high altitudes and later for space capsules drove laboratory research. Practical needs often dominated and applications were made before mechanisms were available to explain observations. Basic laboratory studies were generally inadequate to safely place limits on human tolerances to elevated concentrations and pressures of oxygen. Successes and failures in the practice of oxygen therapy gradually increased safety but also disclosed the falsity of hopes that either oxygen itself or antioxidants were cures for all ailments. The period after the late 1960s onward has been a time of increased focus on understanding the mechanisms of oxygen toxicity and biological, oxidant-stress defenses.

HISTORY OF OXYGEN AS THERAPY

Introduction

From the time of its discovery as an element and its isolation from air, the essential nature of oxygen for animal life was apparent. Early experiments by Joseph Priestley (described in Chapter 2) also provided the basis for speculating that oxygen concentrations above the 21% found in air, might be beneficial. Several physicians were quick to treat patients in chambers filled with compressed air which exposed them to elevated oxygen, and some men died. Practical men exposed workers to breathing compressed air (containing elevated oxygen) for projects including tunneling and bridge constructions before it was proven safe, and more men died. Despite this, largely with trial and error and at considerable risk, oxygen was used and misused for therapy. Today, it is safe and acceptable, and indeed, indispensable therapy for various medical conditions. I can think of no other therapy that has had such a wide and colorful history.

The 1600s

The earliest recorded attempts at oxygen therapy came about in the 1600s by increasing atmospheric pressure with air as the gas in a sealed chamber termed a "domicilium" by a British clergyman named Henshaw (I could not find his first name or biography) [1 - 4]. The domicilium was filled by air (oxygen was not discovered until 1773) pressurized using an old organ bellows. The chamber could be operated at above and below normal atmospheric pressure, and it was sealed and unventilated. It must have been frightening for patients. Henshaw treated his patients who suffered from acute conditions with increased pressure, and those suffering from chronic conditions he blessed with lowered pressure. Insight into his approach to therapy is provided by a quotation [4]:

> “In times of good health this domicilium is proposed as a good expedient to help digestion, to promote insensible respiration, to facilitate breathing and expectoration and consequently, of excellent use for prevention of most affectations of the lungs.”

Scientists also experimented with the effects of reduced air pressure. In 1659 Robert Boyle (1627-1691) commissioned construction of a device he called the “pneumatic engine” (in today’s world, a vacuum pump). He conducted many experiments which he described in a book[2] which has been reproduced [5]. Experiment number 41 (in a series) was designed to demonstrate the requirement of living animals for air to survive. He exposed a variety of life forms including birds, mice, eels, snails and flies. His description of a lark exposed to decreased pressure and lack of oxygen is quaint:

> “…the Bird for a while appear’d lively enough, but upon a greater

CHAPTER 7

Oxygen Biology, Boon and Bane

Abstract: Oxygen paradoxically exhibits both strongly positive and violently negative effects in biological systems. Irwin Fridovich succinctly characterized this as the "boon and bane" of oxygen. Joe M. McCord in Fridovich's laboratory, in 1969, had discovered the enzymatic activity of copper-zinc superoxide dismutase that fueled a revolution in research into the mechanism used by the body to defend itself against the toxicity of oxygen. Superoxide dismutase converts the biologically-active oxygen radical, superoxide, into molecular oxygen and hydrogen peroxide and the latter is a substrate for catalase which is abundant in cells and converts hydrogen peroxide into oxygen and water. Oxygen has been shown to be a vital participant in extremely diverse biological functions including phagocytosis, athletic performance, ageing, mitochondrial energetics, and a host of oxidant stress-related and degenerative diseases which are areas of continuing research today. The mechanisms of oxygen toxicity at the cellular level were primarily speculative until near the end of the 1960s when the significance of oxygen "free radicals" became the dominate research theme. The means to examine the mechanisms of oxidative damage to enzymes, membranes and DNA became available and scientists began to probe into intracellular sites and mechanisms of oxygen toxicity. The realization that various electronically "excited" (free radical forms of oxygen) were the culprits that damaged the vital and sometimes delicate machinery of life was brought into sharp focus by the discovery of superoxide dismutase and its exploration by both pure and applied researchers in medicine, chemistry, biochemistry, and molecular biology. There were controversies, primarily about which oxygen radicals were most significant, but this led to realization that a host of factors including the chemistry and biology of the many oxidized species, iron and other transition metals as electron donors, and complex cellular defense mechanisms were essential parts of the new story that began in the late 1960s and is continuing today.

Keywords: Ageing, Diffusion limited, Fenton reaction, Hydrogen peroxide, Hydroxyl radical, Iron, Irwin Fridovich, Joe McCord, Lipid peroxidation, Mitochondrial respiration, Oxidation-reduction, Oxygen free radical, Peroxidase,

Olen R. Brown

Redox cycle, Singlet oxygen, Superoxide, Superoxide dismutase, Transition metals, Vitamin A, Vitamin C, Vitamin E.

INTRODUCTION

The end of the decade of the 1960s was the beginning of a new era in laboratory studies focused toward understanding the mechanisms of oxygen toxicity at the intracellular level. This research was driven by a desire to understand how oxygen was toxic at the most basic level. Research into toxic mechanisms had progressed that far. It was also necessary to pursue oxygen's toxic mechanisms to better understand what was already discovered about oxygen's role in energy metabolism and, of course, for its safe therapeutic application. The studies being undertaken were also relevant to probe how various chemicals, including therapeutic drugs such as some used to treat cancer, produced harmful side-effects. Oxygen radicals appeared to be involved in how both ionizing and non-ionizing radiation damage cells. Oxidant stress and oxygen free radicals were surely involved in lipid peroxidation, mutations in DNA and damage to protein structure. Understanding the nature and formation of reactive oxygen species—"free radicals"— became an obvious requirement for a deeper understanding of the chemistry of oxygen within cells.

After a brief excursion as prelude to explore catalase, hydrogen peroxide, hydroxyl radical, and superoxide dismutase (their stories are intertwined) I will focus this chapter on cellular mechanisms of the toxicity of oxygen and the biological defense strategies, beginning with the discovery of the function of the enzyme superoxide dismutase.

Hydrogen peroxide is thermodynamically unstable and decomposes to water and molecular oxygen. Biologically, however, it is decomposed with great efficiency by the enzyme catalase which Louis Jacques Thenard (1777-1857) is credited with discovering in 1818. Thenard speculated that an "unknown substance" was responsible for the observed rapid breakdown of hydrogen peroxide. Thenard was the son of poor French peasants but managed to become educated at the academy of Sens and went to Paris at age sixteen to study pharmacy. It is said that he was unable to pay the small regular fee of twenty francs a month and he received a position in the laboratory of the prominent chemist, Vanquelin, only at the intercession of Vanquelin's sisters. He did so well that he became a teacher of chemistry and secured a position at the Ecole Polytechnique and the Faculte des Sciences. After his death a statue was erected in his memory at Sens and subsequently the name of his native village was changed to Louptiere-Thenard. He is famous for Thenard's blue, a coloring matter, based on cobalt, which he discovered that "was capable of withstanding the heat of a porcelain furnace" [1].

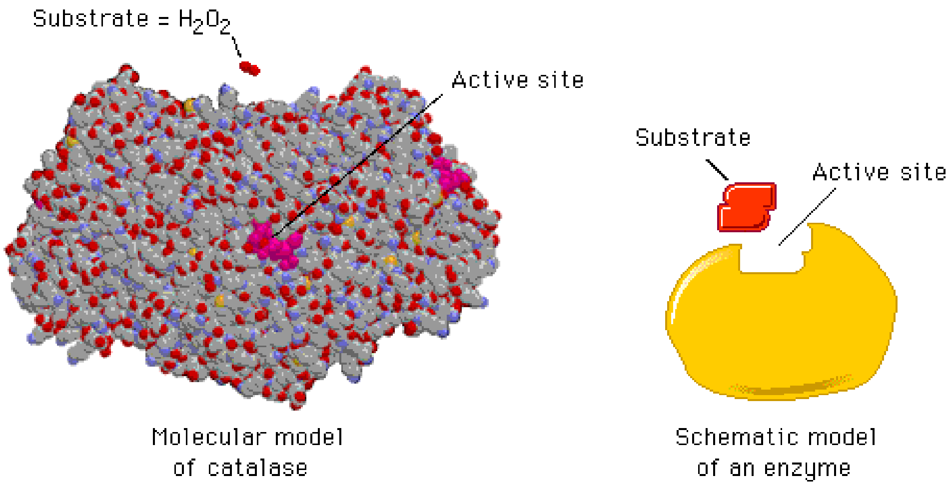

Fig. (1). Catalase (left) is a large protein molecule with a three-dimensional structure containing an active site where the substrate H_2O_2 fits, and is catalytically cleaved to water (diagrammatically shown on the right).

Thenard's biological substance, because of its strong effervescent, was known to be present abundantly in tissues, but its function was not understood. It was named catalase by Oscar Loew in 1900 [2] and it is central to understanding the oxidation-reduction reactions that are fundamental to cell metabolism. It is a catalyst for the breakdown of hydrogen peroxide with the formation of water and oxygen at a greatly accelerated rate (Fig. **1**). This catalytic rate is reported to be up to five million molecules of hydrogen peroxide converted per minute. However, its magic can be better understood by simply saying that this enzyme functions at the maximum theoretically possible rate; the rate dictated by the rate of arrival of hydrogen peroxide molecules by diffusion to the active site of the enzyme and not on the rate of cleavage of hydrogen peroxide by the enzyme. There are more than

CHAPTER 8

Oxygen Transport to Lung to Blood to Spark of Intelligence in the Brain

Abstract: The human body contains coordinated, complex components that work together to efficiently extract oxygen from the air and deliver it to the intracellular sites where it is essential for life. Oxygen's journey for life begins in the lung where it is transported by a system of branching tubes of decreasing size, the bronchus, bronchioles and bronchi. The lungs are made of a wonderful collection of cells that are organized into a unique, spongy tissue that contains the bronchial tubes with air sacs, the alveoli, at their termini. The interior surface area of the alveoli, collectively, is equal to the area of a tennis court. An intricate system of blood capillaries, arteries, and veins envelops each alveolus and circulates a large supply of blood that arrives deoxygenated and leaves oxygenated. The lung works efficiently by using air pressure and diaphragm muscles to expand and decrease lung volume during breathing. Oxygen is not sufficiently soluble in blood to supply the body's needs. However, a complex oxygen-carrying molecule, hemoglobin, is packaged into special cells, the red corpuscles where truly magnificent biochemistry reigns. The process works, by analogy, like a subway system to load and unload oxygen and carbon dioxide from alveoli to cells throughout the body. Hemoglobin does double duty and reverses the sequence by loading carbon dioxide from tissues and unloading it in alveoli. The heart supplies the pumping force that moves the red cells which arrive at ever smaller arteries and then to capillaries which intercalate with tissues that must have a continuous supply of oxygen to function. All cells require oxygen to supply the bulk of their energy needs, and some for other purposes, but the brain is especially oxygen hungry and uses approximately 25% of the total resting needs by the body for oxygen. Working muscle is provided with hemoglobin's cousin, myoglobin, which can store oxygen and release it to contracting muscle cells. Oxygen is nearly perfect for bioenergetics and it also has the right stuff to be efficiently transported.

Olen R. Brown

Keywords: Alveolus, Anoxia, Aorta, Asthma, Atelectasis, Bronchial tubes, Glyceraldehyde phosphate, Hemoglobin, Hypoxic, Myoglobin, Oxygen, Oxygen radicals, Plasma oxygen concentration, Red corpuscles, Regulation, Respiration, Surfactant, Vena cava.

INTRODUCTION

Oxygen is ideally suited for cellular respiration. No other molecule has the unique set of characteristics that provide the balance that allows oxygen to be transported to cells, to safely (for the most part) participate in oxidation-reduction reactions, and to capture and remove waste carbon as CO_2. Chlorine and fluorine are small, similar, gaseous molecules but they poison biological systems. Oxygen, as a diatomic molecule is generated by photosynthesis and maintains a steady concentration in the atmosphere. The lungs of multicellular land animals remove it efficiently from air and the gills of aqueous creatures extract it effectively from water. The energy required for this is a manageable loss. Oxygen is insufficiently soluble in water, but hemoglobin and myoglobin transport it efficiently, with provisions to attract oxygen in the lungs, and release it in tissues. The circulatory system can move oxygen, when it is safely bound to hemoglobin packaged in red cells, about the body and deliver it to cells. At the intracellular level, oxygen has the properties of "biological dynamite"; safe enough to use, but capable of a controlled, "cold" burning (oxidation) of fuel to provide (as ATP) the energy needs of cells. At the smallest subatomic scale, the electron arrangement of oxygen permits efficient flow of electrons to sustain energetics with production of water and CO_2 as safe, biologically non-polluting, waste products. The above is an oversimplification but establishes that oxygen, and no other atom or molecule, is capable of sustaining life as we know it on earth.

THE LUNG

Oxygen begins its journey to sustain biological respiration in land animals including humans as an inspired gas from air. The circumstances are initially different for creatures that live in water, but we will focus on air-breathing; the subsequent biochemical processes are similar for all multicellular aerobic creatures. The human lung is efficient; respiration is driven by a simple movement of diaphragm muscles that expand the chest cavity and air pressure does the rest to fill the lungs. Relaxation of the diaphragm muscles expels the air efficiently (Fig. **1**). Oxygen, a low molecular weight gas, is respired efficiently. Its air concentration (approximately 21%) allows efficient metabolism; slightly lower oxygen concentrations significantly impair metabolism and at approximately 2- to 3-times the air concentration, oxygen is toxic. Also, many substances would spontaneously combust or burn at room temperature if air were pure oxygen.

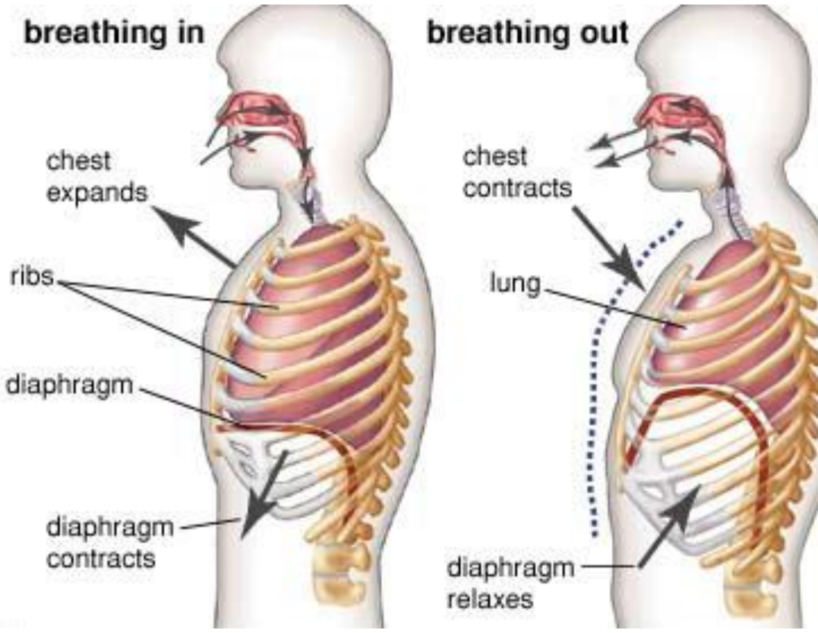

Fig. (1). The mechanism of human respiration.

During human respiration, air is drawn in down a series of branching tubes that decrease in size to the level of the alveolus in the lung (Fig. (**2**), left panel). A debilitating disease, asthma, occurs when bronchioles become inflamed and swollen with narrowing of the passageway for oxygen transport (Fig. (**2**), right panel). The inflammation may involve oxidant stress mechanisms.

Relationships among anatomical features of the respiratory system are detailed in Fig. (**3**) on the following page. Inspired air arrives at the termini of the smallest, branching bronchioles and enters small sacs, the alveoli, which are shown in

CHAPTER 9

Oxygen: Parkinson's, Alzheimer's, Huntington's

Abstract: Parkinson's, Alzheimer's, and Huntington's are degenerative brain diseases with some similarities in symptoms. Oxidative stress has been linked to these diseases, but causation is unproven. Dementia is a central feature but is not diagnostic. Based on historical, clinical descriptions the order of discovery as a disease is: Parkinson's (1817), Huntington's (1842) although it probably has been known since the Middle Ages and was called "chorea", and Alzheimer's (1906). Alzheimer's is the most common; Parkinson's is second; and Huntington's is the third most common neuronal, degenerative disease. None of these diseases can be cured, and there is generally a long, severe decline in functional ability that is tragic for the individual, the family and friends. Although the causes of these diseases are unknown, there are genetically inherited risks for each. The pathophysiology, brain sites affected, cellular and sub-cellular mechanisms, and genetics for each disease is complex and oxidant stress has been incriminated for some aspects of these diseases. Parkinson's results in a progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the metabolism of dopamine itself generates reactive oxygen species. Therapy with the dopamine precursor levo-dopa (dopamine does not pass the blood- brain barrier) does not provide lasting benefits. Speculation that Parkinson's disease is caused by reactive oxygen species generated from pesticide exposure has not been proven. Discoveries by co-workers in my laboratory pointing to special sensitivity from oxidant stress for certain iron-containing enzymes in amino acid metabolism are promising links to oxidant stress causation. Generation of oxidant stress *via* aberrant mitochondrial oxidative metabolism is a viable thesis but a cure for these diseases is not in sight and is more likely to result from future discoveries using stem cells and perhaps gene therapy.

Keywords: Age-related neurodegeneration, α-synuclein, Alzheimer's, β-amyloid deposits, Cellular redox balance, Dopamine, Gene mutation, Huntingtin gene, Huntingtin protein, Huntington's, Kynurenic acid, Kynurenine pathway, Levo-dopa, Lewy bodies, Miss-folded proteins, Oxidant stress, Parkinson's, Protein phosphorylation, Quinolinic acid, ROS, Tau, Tryptophan metabolism.

Olen R. Brown

INTRODUCTION

Age-related brain degeneration occurs in Parkinson’s, Alzheimer’s, and Huntington’s diseases and there are links to genetic defects, most importantly for the latter. There is evidence that oxidative stress mechanisms are involved in the brain degeneration that is characteristic of each disease. The hereditary basis of Huntington’s disease was discovered in 1993, and its hallmark is a mutated huntingtin protein, that is toxic to brain cells with damage most evident in the striatum early in the disease which then spreads to other areas which are conspicuously affected. Alzheimer’s disease is characterized by shrinkage of the total brain, and by the formation of twisted aggregates of the tau protein to form neurofibrillary tangles within neurons, and the deposition of another protein, β-amyloid, in spaces between brain cells. Parkinson’s disease results primarily from death of dopamine-producing cells selectively in the substantia nigra pars compacta. These diseases progress in severity; they are deeply tragic for the patient, family members and friends; and current therapies are limited and no cures are available.

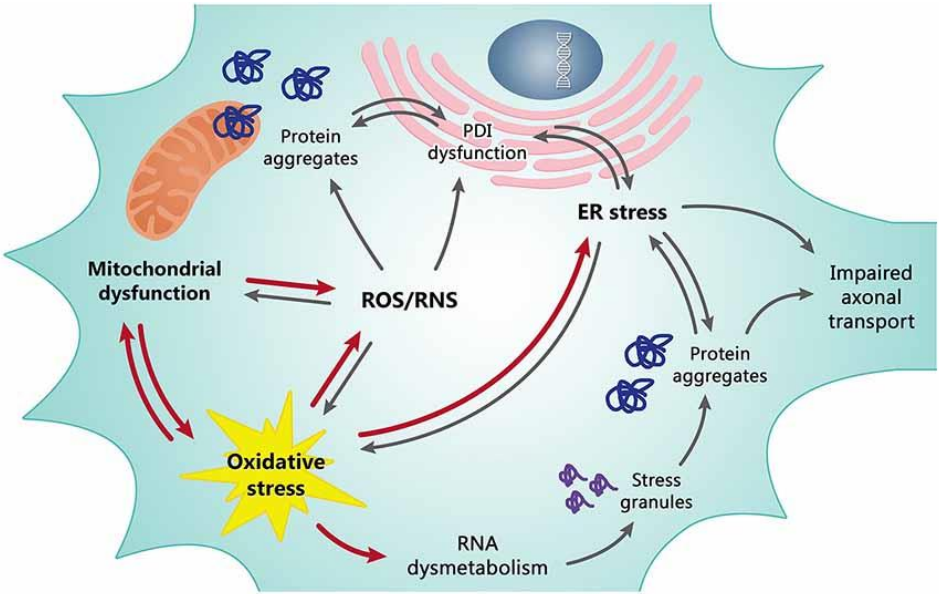

Fig. (1). Oxidative stress and brain dysfunction.

OXIDANT STRESS

Excessive oxidative stress can result from dysfunctions in mitochondrial oxygen utilization, redox cycling of certain xenobiotics and some therapeutic drugs, and other mechanisms that generate a variety of redox-active species. Fig. (**1**) depicts the complexity of proposed interactions that connect generation of oxidative stress and damage to the brain, with a focus on Parkinson's disease.

PARKINSON'S DISEASE

Introduction

Parkinson's disease results from selective death of neuronal cells in an area of the mid-brain called the substantia nigra pars compacta. The neurons that die contain the neurotransmitter dopamine and the neuronal processes extend into the striatum of the brain. The affected neurons control voluntary movement and their degeneration leads to the four cardinal debilitating symptoms of Parkinson's disease: resting tremor, muscular rigidity, bradykinesia, and postural imbalance [1]. In over 90% of cases the cause of the disease is not known, but aging is a strongly-associated factor and the incidence of Parkinson's disease increases exponentially with age after 65 [1, 2]. Genetics has a role in the disease and mutations in a number of genes have been identified. In both idiopathic and genetically-related Parkinson's disease, oxidant stress has been implicated [1 - 6].

James Parkinson[2] (1755-1824) (Fig. **2**) first described in 1817 the basic, clinical symptoms that characterize Parkinson's disease. More than a century passed before the basic pathology was determined to be the loss of neurons in the substantia nigra pars compacta. Progress into the nature of the disease accelerated when Arvid Carlsson (1923-) discovered dopamine in the brain, and this was followed by the anatomical elucidation of the nigrostriatal dopaminergic pathway and discovery that loss of neurons in this region led to striatal dopamine deficiency (responsible for the major symptoms of the disease) and subsequently that oral administration of the dopamine precursor levodopa alleviated symptoms [6]. Carlsson was awarded the Nobel Prize in Physiology or Medicine (shared with two others) "*… for their discoveries concerning signal transduction in the nervous system"*[3].

CHAPTER 10

Oxidant Stress: Cardiovascular and Lung Disease, Exercise, and Aging

Abstract: Oxygen utilization by essential metabolic processes inevitably has the potential to damage or destroy essential cell components by oxidative mechanisms. This negative effect of oxygen is called oxidant stress. Over a lifetime oxidant stress contributes to the decreased functioning observed by aging; it occurs during exercise with both detrimental and adaptive potential; and it is associated with or causative for certain lung and cardiovascular diseases. Oxygen uptake and utilization becomes maximal during athletic performances with high workloads for extended time periods. The associated oxidative stress is positive in outcome *via* enhanced antioxidant defenses. There is sufficient evidence that the primary source of excess oxidant stress is at the site of oxygen utilization at the inner membrane of mitochondria. Normally, a small fraction of mitochondrial use of oxygen is diverted from the secure transfer, one at a time, of electrons *via* the cytochrome system to generate water and ATP in a complex, carefully orchestrated process. Four electrons are required to reduce diatomic oxygen completely and partially reduced intermediates, including peroxides, and the free radicals superoxide and hydroxyl radical can form. Oxidative damage occurs, and damaged mitochondria can produce even more free radicals. There are also other biochemical sources and mechanisms that generate oxidative radicals and create oxidant stress. The lung, which is exposed to the highest concentration of oxygen, is especially vulnerable to oxidant stress when hyperoxia is used therapeutically. Lipid membrane damage involving the alveoli, and potentially fibrosis, is a consequence for premature infants and for chronic obstructive pulmonary disease and other lung pathologies in adults. Oxidation of LDL-cholesterol by oxygen free radicals during excess oxidant stress is the initial event in a sequence leading to atherosclerosis and potentially to cardiovascular events and strokes. A natural balance of antioxidant defenses is protective for oxidant stress and is enhanced by antioxidants in the diet and as a positive benefit from exercise. However, there is evidence that, over time, the net effect of oxidant stress contributes to detrimental deteriorations associated with the aging process in the brain and throughout the body.

Olen R. Brown

Keywords: Aerobic metabolism, Aging, Anaerobic metabolism, Atelectasis, COPD, Environmental factors, Exercise, Fibrosis, Foam cells, Genetics, LDL-cholesterol, Longevity, Macrophage, Maximum oxygen uptake, Monocyte, Oxidant stress, Plaque, Prematurity, Second messenger, Supplements.

INTRODUCTION

Oxidant stress, resulting from the necessary biochemistry that occurs in the body is the common thread that connects the subjects of exercise physiology, aging, and certain pathologies in the lung and cardiovascular system described in this chapter. Of course, oxidant stress does not fully explain all the pathology seen in all the medical conditions addressed in this chapter. It would also be incorrect to infer that oxidant stress, however defined, is the singular cause for each of these conditions. However, oxidant stress is an inevitable result of the body's use of oxygen: its transport; oxidative phosphorylation to produce ATP at the mitochondrial level; and redox-reactions that can damage essential molecules and even complex structures in cells. The latter includes: genes, chromosomes, DNA, and associated regulatory factors; proteins functioning as enzymes and essential structural components; the broad group of cellular components that have lipids as components; and other molecules that do not fit easily into defined categories biochemically. Obviously, the topics chosen for this chapter are vast in scope and complexity. Focusing on the role of oxidant stress is not intended to be a clarion call that all answers lie at the doorstep of oxygen.

Some level of oxidant stress in the body is appropriate. A medical dictionary definition is useful as a beginning. Oxidant stress has been defined [1]: "Physiological stress on the body that is caused by the cumulative damage done by free radicals inadequately neutralized by antioxidants and that is held to be associated with aging". The emphasis on aging is appropriate; it indicates that oxidant stress is cumulative and may increase sequentially. In the context of the four areas of this chapter, the stated definition obviously requires broadening.

Normal Level of Oxidative Stress

It is reasonable, given the chemical nature of oxygen and the labile nature of the biological components of living systems that some untoward consequences will occur. One important site (Fig. **1**) is the mitochondrion where oxygen is utilized to bioenergetically produce ATP (oxidative phosphorylation). This site functions in nearly all cells in the body. There are other sources of oxidant stress and the body has an elaborate compensatory system designed to prevent unwanted oxidation and to reverse or restore oxidative damage that does occur.

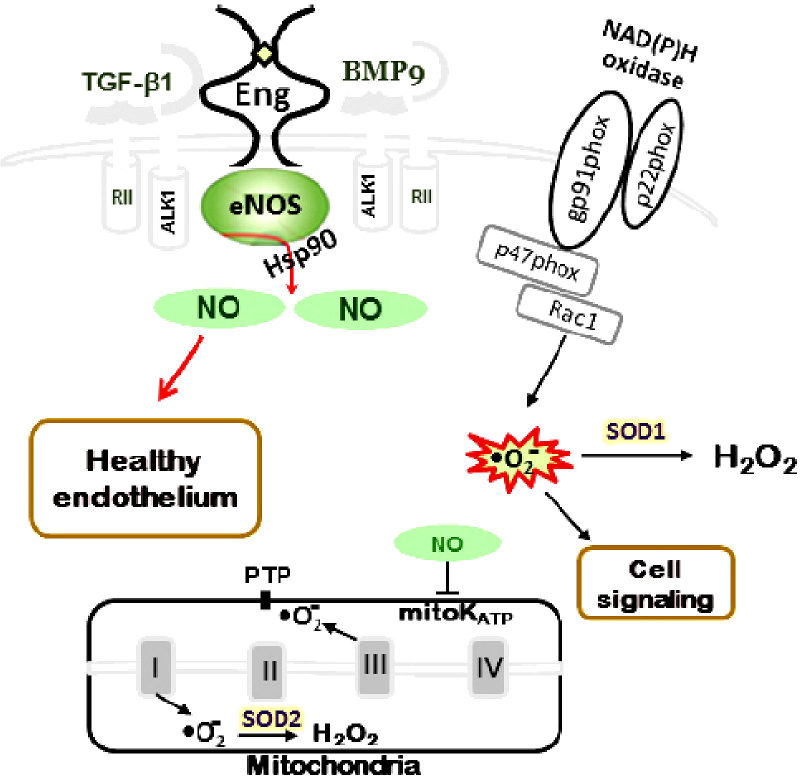

Fig. (1). Sites of oxidant stress at the mitochondrial level.

OXIDATIVE STRESS AND CARDIOVASCULAR DISEASE

A brief overview of biological production of oxygen radicals is useful; for additional details refer to Chapter 7. In the early 1930s Fritz Haber (1868-1934) and Joseph Weiss (1905-1972) proposed that hydroxyl radicals were produced by a reaction of superoxide and hydrogen peroxide. Subsequently this came to be known as the Haber-Weiss reaction. Haber, a German Chemist, was awarded the Nobel prize for Chemistry in 1918 for discoveries related to nitrogen fixation [2].

CHAPTER 11

Oxygen: The Future

Abstract: Oxygen has had a long history; it was the 18th element to be discovered of 118 known elements, of which 28 have been created artificially. Oxygen is essential for all aerobic life on earth and pure oxygen at various partial pressures and mixed with other gases is used as a medicine for conditions where the oxygen supply is inadequate, including for premature infants whose lungs are not completely developed. Oxygen is also used for pathologies where oxygen supply to tissues is compromised. Oxygen is a component in gas mixtures used for deep-water diving for sport, recreation, salvage, exploration and mining. Oxygen is a requirement for manned space flight and commercial air travel. In the future, it is a certainty that all of these uses and requirements will continue. It is almost as sure that things now predictable based on past and current research and things as yet unimagined are destined to happen in the future. For therapy, it is probable that artificial blood that adequately perfuses the body will be routine. For recreation, it is likely that private oxygen chambers will get fancier and be more widely used, as will oxygen as a novelty is “sports” bars. In sports, the use of oxygen in breathing mixtures for deep-sea diving and by free divers will continue although it is difficult to see how current records can be much extended. Artificial gills will never become practical but by mimicking sea mammals, man may become as free as dolphins to explore the deeps. For endurance sports and sprints, oxygen supplementation, particularly for training recovery and its psychological effect, will become common and contribute to new records. Ways to manufacture oxygen cheaply and reliably will make possible undersea habitats that will include underwater cities. As future therapy, antioxidants and other oxidant stress protector molecules will allow expanded therapies for many conditions which are limited by the toxicity of oxygen. The most spectacular advance will be in artificial photosynthesis that will remove carbon dioxide from the atmosphere, provide oxygen and carbon-based fuels and power cells that will far outstrip solar cells.

Keywords: Artificial blood, Artificial photosynthesis, Aquarius, Biosphere 2, *Chlorobiaceae*, CRISPR, Deep water diving, Dubai underwater hotel, Gills,

Olen R. Brown

Habitats, Hyperbaric chambers, ISSHL, Lagrangian point, Myoglobin, Ocean spiral, Oxidative stress, Perfusion, Space cities, Sports bars, Underwater mining, Whales.

INTRODUCTION

Oxygen is one of either 90 or 92 (depending on who is counting) "natural" elements found on the earth. There are additional elements that are man-made and which have very short half-lives, that bring the total to currently 118. Oxygen was the eighteenth element to be officially discovered (which occurred in 1774). Several elements including gold, silver, iron and copper (credited as having been known longer than any other element) were known from antiquity with no specific date of "discovery" recorded [1, 2].

Writing about the future of oxygen necessarily involves thoughts about: what we may expect to learn about the chemistry and biology of the molecule, new approaches and technologies for oxygen therapy, oxygen as it relates to the nano world, and breathing gas requirements for space and undersea habitats. Predicting these discoveries, applications and uses is only safely done if they are the immediate future and based on small steps beyond the present perception, or if they are so far in the future and so fanciful as to not be considered seriously or detrimentally to the credit of the dreamer, should they never happen.

FRONTIER OF PHYSICS, CHEMISTRY AND BIOLOGY OF OXYGEN

The basic chemistry and biology of oxygen has been thoroughly explored. The mechanisms within the cell for the metabolism of oxygen have been described. Oxidant stress and biological defenses against harmful effects are known in considerable detail. Formation of oxygen radicals in biological systems is understood. The details of second messengers and subsequent consequences in terms of damage and repair are only beginning to emerge. There will be new discoveries of how the oxidation-reduction state of the cell is controlled including in different tissues in physiologically normal and diseased states. Since the work of Otto Warburg, it has been appreciated that oxidative metabolism may hold one of the keys to defeating cancer cells and the current state of knowledge is ripe for such research. Some xenobiotics are toxic *via* a free radical mechanism involving oxygen. There is the likelihood that new drugs that are protective and new ways to stimulate anti-oxidant cellular defenses will advance both cancer chemotherapy and antidotes for poisons that work by this means.

Areas Ripe for New Discoveries

A most exciting prospect for the near future are discoveries, at the margins of physics and chemistry, relating to the quantum behavior of the electrons set free from oxygen and their participation in various biological systems. These systems include photosynthesis, where artificial photosynthesizing components have already been designed [3]. It is reasonable that these designed systems will be partly derived from biological systems and partly artificial. Since oxygen is produced, and carbon dioxide is consumed, they have great ecological potential. They also result in generation of reduced organic molecules and these have various uses as food, fuel, and starting chemical for synthesis including plastics. The potential for artificial photosynthesis is truly enormous. Initial efforts will be toward making the systems more durable and more efficient at transferring energy from light into carbon-based chemistry. This is where greater understanding of the quantum behavior of oxygen's electrons is required and it will be the focus of research that brings together biologists, chemists and theoretical physicists. Increasing the efficiency of energy transfer is one key to successful applications and resonance effects of entangled electrons will be a focus of discovery designs. A second essential will be durability and extended temperature of operation and this is where improvements will be sought in the biological components of systems. New advances in 3-D printing will be ideally suited to applications of this system for artificial photosynthesis to remove carbon dioxide from the atmosphere and for creating useful energy that will be more efficient than current solar energy devices. In the future, many new carbon-based by-products will be produced, some as starting chemicals for a variety of chemical syntheses. Biodegradable plastics will likely be an early, successful product application.

Synthetic photosynthesis will produce oxygen as a by-product which together with the energy and carbon-based compounds produced will have applications for the undersea and outer space habitats that I shall subsequently address.

It is predictable that mechanisms to selectively and specifically make point

SUBJECT INDEX

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