Oxygen

The Molecule that made the World

Chapter 1: Elixir of Life and Death

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About

Dr Nick Lane is a British biochemist and writer. He was awarded the first Provost's Venture Research Prize in the Department of Genetics, Evolution and Environment at **University College London**, where he is now a Reader in Evolutionary Biochemistry. Dr Lane's research deals with evolutionary biochemistry and bioenergetics, focusing on the origin of life and the evolution of complex cells. Dr Lane was a founding member of the UCL Consortium for Mitochondrial Research, and is leading the UCL Research Frontiers Origins of Life programme. He was awarded the 2011 BMC Research Award for Genetics, Genomics, Bioinformatics and Evolution, and the 2015 Biochemical Society Award for his sustained and diverse contribution to the molecular life sciences and the public understanding of science.

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Chapter 1: Elixir of Life and Death

OXYGEN DEFIES EASY CLASSIFICATION. Ever since it was discovered in the 1770s, its properties and chemistry have been squabbled over by scholars and charlatans alike. The controversy persists today. Oxygen is hailed as the Elixir of Life, a wonder tonic, a cure for ageing, a beauty treatment and a potent medical therapy. It is also purported to be a fire hazard and a dangerous poison that will kill us in the end. The popular health press is contradictory. Inhaling pure oxygen in cosmopolitan ‘oxygen bars’ and health clinics is said to work wonders, yet the opposite, ‘high-altitude therapy’, is claimed to eliminate superfluous oxygen, conferring the health benefits of austerity. So-called ‘active’ oxygen treatments, meaning ozone and hydrogen peroxide, are touted as miraculous scourges, or as cures for cancer; yet at the same time we are told that the secret of a long life is to eat plenty of antioxidants, to protect us against the very same ‘active’ forms of oxygen. Oxygen seems to attract nonsense and misinformation like a magnet.

However muddled these accounts, they agree about one thing: oxygen is important. After all, if we stop breathing it, we will be dead in minutes. Our bodies are beautifully designed to deliver oxygen to each of 15 trillion cells every second. All the symbolism of red blood ultimately rests in the simple chemical bonding between oxygen and haemoglobin in our red blood cells. Suffocation and drowning – the physical deprivation of oxygen – are among the darkest of human fears. If we think of a planet without oxygen, we think of a sterile place pockmarked with craters, a place like the moon or Mars. The presence of oxygen in a planetary atmosphere is the litmus test of life: water signals the potential for life, but oxygen is the sign of its fulfilment – only life can produce free oxygen in the air in any abundance. If pressed for an unemotional reason for not cutting down the rain forests or polluting the oceans, we may argue that these great resources are the ‘lungs’ of the world, ventilating the Earth with life-giving oxygen. This is not true, as we shall see, but illustrates the reverence in which we hold oxygen. Perhaps it is not entirely surprising that we seek mystical or healing properties in a colourless, odourless gas.

This book is about life, death and oxygen: about how and why life produced and adapted to oxygen; about the evolutionary past and future of life on Earth; about energy and health, disease and death, sex and regeneration; and about ourselves. Oxygen is important in ways that most of us hardly even begin to imagine, ways that are far more fascinating than the loud claims of health features. But before we begin our journey, we need to mark out the playing field. Is oxygen an elixir, or a poison, or both? And how can we tell the difference? The easiest way to find out is to go back in time, to the beginnings of our own understanding….

…. The toxicity of oxygen is slow-acting, or hidden from view, in normal circumstances. Many people receive oxygen therapy in hospital, or spend days, sometimes weeks, in oxygen tents, or inhale oxygen in bars with no ill effects. Astronauts often breathe pure oxygen for weeks on end, though in space the capsule is pressurised to only one third of atmospheric pressure, which makes it equivalent to breathing 33 per cent oxygen. This distinction explains why the three astronauts were killed on Apollo 1 in 1967, as they were completing tests on the ground. In space, the inside of the capsule is always pressured to a higher pressure than the surrounding vacuum, which means that spacecraft are built to withstand a greater pressure inside than outside. To maintain this pressure differential, Apollo 1 was pressurised to above atmospheric pressure whilst on the ground. Unfortunately, the spacecraft was still being ventilated with pure oxygen. Instead of breathing the equivalent of 33 per cent oxygen, then, the astronauts were actually breathing six times the normal 21 per cent oxygen (the equivalent of 130 per cent oxygen). In this oxygen-rich atmosphere, a spark from the electrical wiring led to an uncontrollable fire, that reached a temperature of 2500°C within minutes.

But oxygen is more than just a fire risk: it is toxic to breathe. This toxicity depends on the concentration and duration of exposure. Most people can breathe pure oxygen for a day or two, but we cannot breathe it for longer than that without risk. If the concentration of oxygen is increased even more by compressing the gas, then the toxic effects become dramatic.

The shocking realisation that oxygen is toxic came from the experiences of the earliest scuba divers, towards the end of the 19th century. (The word scuba was a later coinage, and stands for self-contained underwater breathing apparatus.) Scuba divers were vulnerable because they carried their breathing apparatus with them, and usually breathed pure oxygen. The oxygen in the apparatus could be compressed by water pressure. Breathing pure oxygen at depths below about eight metres causes seizures similar to an epileptic grand-mal – a disaster if the diver loses consciousness underwater.

Oxygen convulsions were first described systematically by the French physiologist Paul Bert, who succeeded Claude Bernard as professor of physiology at the Sorbonne in Paris. In his celebrated 1878 monograph on barometric pressure, Bert discussed the effect of oxygen on animals subjected to different pressures in a hyperbaric chamber. Very high oxygen concentrations caused convulsions and death in a matter of minutes. The following decade, in 1899, the Scottish pathologist James Lorrain Smith showed that lower levels of oxygen could have an equally deadly, but delayed, effect. Animals exposed to 75 per cent oxygen or more (at normal air pressure) had such serious inflammation of the lungs after a few days that they died. For this reason, oxygen dosages in hospitals are always strictly controlled. Convulsions and lung injury became familiar worries to scuba divers, however. Both Paul Bert and James Lorrain Smith are still commemorated in diving terminology. Unfortunately for Smith, his unusual name, along with his habit of styling himself J. Lorrain Smith, frequently turns the tribute into the ‘Lorraine Smith’ effect.

While many divers were careful not to dive too deep while breathing pure oxygen, the Navy could not always afford to be so cautious. In the Royal Navy Submarine Escape Handbook, published in 1942, seamen were instructed to watch out for the symptoms of oxygen poisoning: “tingling of the fingers and toes, and twitching of the muscles (especially around the mouth); convulsions followed by unconsciousness and death if a remedy is not taken.” Naval divers during the war invented a mythical monster, Oxygen Pete, who lurked at the bottom of the sea waiting to molest unwary divers. Oxygen toxicity ‘hits’ during this time were referred to as “getting a Pete”.

A more rigorous understanding of oxygen toxicity, human limits and gas mixtures was clearly needed, and JBS Haldane was commissioned by the Royal Navy to follow in the footsteps of his dive-physiologist father. Always an advocate of being one’s own rabbit, Haldane subjected himself and his colleagues to various oxygen concentrations under different pressures, noting how long it took before convulsions set in. Exposure to pure oxygen at seven atmospheres pressure led to convulsions within five minutes. He later wrote that:

“The convulsions are very violent, and in my own case the injury caused to my back is still painful after a year. They last for about two minutes and are followed by flaccidity. I wake in a state of extreme terror, in which I may make futile attempts to escape from the steel chamber.”

Nonetheless, his efforts were successful. The Royal Navy secretly developed various nitrogen/oxygen (nitrox) mixtures, which lowered the risk of both oxygen toxicity and nitrogen narcosis (the ‘bends’). These nitrox mixtures were used by British commandos defending Gibraltar in the Second World War, and were kept such a tight secret that even the US Navy did not find out until the 1950s. Using nitrox mixtures the British divers could operate at greater depths. A major element of British strategy was to lure the combatants into deep waters until they were overwhelmed by convulsions. Mugged by oxygen: perfidious Albion indeed!

BREATHING OXYGEN AT HIGH CONCENTRATION is obviously toxic. Above about two atmospheres of pressure, pure oxygen causes convulsions and sometimes death. Oxygen accounts for about a fifth of atmospheric pressure, so pure oxygen at two atmospheres pressure is ten times our normal exposure. At lower concentrations, oxygen is unlikely to cause convulsions, but breathing pure oxygen for a few days can still cause life-threatening lung damage (this is five times our normal exposure). Such serious inflammation of the lungs prevents us from breathing properly. Ironically, we cannot pass oxygen into the blood stream, so we actually die from oxygen starvation to the rest of the body. At lower levels of oxygen (40 or 50 per cent oxygen, or about twice our normal exposure), the lungs can normally withstand injury and continue to function, though they may become damaged in the end. In these circumstances, the rest of the body adapts by slowing down the heart beat and producing fewer red blood cells. These adaptations are the opposite of the changes that take place at high altitudes to oxygen deprivation. The result, in both cases, is that the tissues receive the same amount of oxygen as before, no more nor less. Such adaptations illustrate the importance of unchanging oxygen levels in the body. They also mean that we cannot gain any long-term benefit from either high or low levels of oxygen, except when we are sick and pathologically oxygen-deprived.

I imagine that most people are comfortable with the idea that too much oxygen can be bad – in effect, that it is possible to have too much of a good thing. Similarly, there is nothing challenging about the idea that we respond to moderate perturbations by re-establishing the physiological status quo. It is a very different proposition to say that 21 per cent oxygen is toxic and will kill us in the end. This is as much as to say that, despite millions of years of evolution, we still cannot adapt to the concentration of oxygen that nature has provided for us. This statement is counter-intuitive to say the least, yet it is the basis of the so-called ‘free radical’ theory of ageing. In essence this theory argues that ageing, and so death, is caused by breathing oxygen over a lifetime. Oxygen is thus not only necessary for life, but is also the primary cause of ageing and death.

Many people have heard of free radicals, even if they have a hazy idea of what they actually are. Most free radicals of biological importance are simply reactive forms of molecular oxygen, which can damage biological molecules (we will consider them in detail in Chapter 6). Regardless of whether oxygen causes convulsions and sudden death, or slow lung damage, or ultra-slow ageing, it always acts in exactly the same way: all forms of oxygen toxicity are caused by the formation of free radicals from oxygen. As the great alchemist Paracelsus said, the poison is in the dose. Convulsions are caused by a massive excess of free radicals acting on the brain, lung damage by a smaller excess acting on the lungs. But free radicals are not just toxic. Fire is impossible without free radicals. So too is photosynthesis or respiration. We can only extract energy from food and oxygen by producing free radical intermediates. The secret to all the chemistry of oxygen, whether we think of it as 'good' or 'bad', is the formation of free radicals.

As conventionally stated, the idea that breathing oxygen causes ageing is disarmingly simple. We produce free radicals continuously inside every cell of our body by respiration. Most of these are 'mopped up' by antioxidant defences, which neutralise their effects. The trouble is that our defences are not perfect. A proportion of free radicals slips through the net and these can damage components of cells and tissues, such as DNA and proteins. Over a lifetime, the damage accumulates gradually until it finally overwhelms the ability of the organism to maintain its integrity. This gradual deterioration is known as ageing.

According to this conventional, if simplistic, explanation, the more antioxidants we eat, the more we can protect ourselves against free radical damage. This is why fruit and vegetables are good for us: they contain lots of antioxidants. Nowadays, many people supplement their diet with potent antioxidants in the belief that their diet cannot provide an adequate supply. The implication is that if we eat enough of the right kind of antioxidants, we can postpone ageing and the diseases of old age indefinitely. This has been touted as 'the antioxidant miracle'.

The truth is rather more complicated, but far more interesting. I shall argue that oxygen free radicals do cause ageing, but that the implications are almost exactly the opposite of what we might expect. We will never extend our lives significantly, to 150 or 200, by loading ourselves with even the most potent antioxidant supplements. On the contrary, antioxidant supplements might actually make us more vulnerable to some diseases. Antioxidants are bit players in the large cast of adaptations that life has made to the presence of oxygen in the air. We can only understand their role if we consider them in the context of the play as a whole. The response of life to the threats and the possibilities of oxygen include adaptations which have had the most profound consequences.

Let me give a few examples. Take photosynthesis, the formation of organic matter from sunlight by plants and algae, which today supports almost all life on Earth. Photosynthesis probably evolved because life had first been forced to deal with oxygen free radicals produced by ultraviolet radiation. This may explain why life took off on Earth but never did on Mars. Take large animals and plants, the distinguishing feature of life on Earth (even if life is found on Mars, we can be virtually sure it will be microscopic). The first multicellular organisms probably evolved from clumps of cells which clustered together to shelter against the rising tide of atmospheric oxygen. Without the threat of oxygen toxicity, life would never have advanced beyond a green slime. Even gigantism relates to oxygen. Giant size offers an escape from the threat of oxygen, and explains the evolution of monster dragonflies, with a wingspan as broad as a seagull, and possibly the rise and fall of the dinosaurs. Now think about sexes. Why should there be only two sexes? Why not one, or three, or many? The evolutionary origin of two sexes may have been a way of coping with oxygen. Babies can only be born young if they are born of two sexes, otherwise oxygen causes the birth of degenerate offspring, destined to age prematurely. This may explain why cloned animals tend to die young. Dolly the sheep, for example, already has arthritis at the age of five, betraying a ‘real’ age of eleven. Finally, think of powered flight. Birds and bats have exceptionally long lives. Why? Flying demands metabolic adaptations to oxygen that also confer a long lifespan. If we want to extend our own lifespan, we must look to the birds.

These are grand statements, which I shall explain and defend later in the book. They are all part of our journey to find out how oxygen affects our own lives and deaths.

THIS IS UNASHAMEDLY A BOOK ABOUT SCIENCE. It is far from a catalogue of dry facts about how the world works, but a book full of quirks, experiments, oddities, speculations, hypotheses and predictions. Science is often presented as facts, frequently in short sound-bites. The scientific method is described as a methodical unravelling of 'the truth', which I imagine must bore most people to tears. The impression that science gives access to an objective reality sets it up in opposition to religion as an ethical system and lends scientists an air of preaching. Too often scientific 'facts' turn out to be wrong or misleading – we are told that there is 'no risk' of a Frankensteinian disaster, only to see it come true before our eyes. At other times, scientists squabble about the meaning of obscure research findings, discrediting their colleagues in public. It is hardly surprising that the general public views science and scientists with growing scepticism. Apart from the unfortunate schism this opens up in society, it means that fewer young people dream of becoming scientists. This is a tragedy. I wonder if the tragedy might be averted to some extent if people had a better idea of the workings of science – of the fun, creativity and adventure.

The real interest of science lies in the unknown, the excitement of charting new terrain. Poking around in the unknown rarely generates a perfect picture of the world – we are more likely to construct a kind of mediaeval map, a distorted but recognisable picture of reality. Scientists try to link together the contours of a story through experiments that fill in a detail here or there. Much of the joy of science lies in devising and interpreting experiments that test these hypothetical landscapes. I have therefore been careful to explain the experiments and observations that underpin the story of this book. I have tried to show how it is that science can be interpreted in different ways, and have presented the evidence itself, along with its flaws, so that you may judge for yourself whether my own interpretation is convincing. I hope this approach will help you to share the spirit of adventure along the border of the known and the unknown.

Science, then, generates hypotheses based on evidence that is specific but limited in scope – islands of knowledge in a sea of unknowing. Very often, individual results only make sense when seen in the context of a bigger picture. In scientific papers, the purpose of the discussion section is to place the new results in perspective. There is a drawback, however, in that science is nowadays highly specialised. It is rare for a medical researcher to refer to the studies of geologists and palaeontologists, or for a chemist to be much concerned with evolutionary theory. For most of the time this matters little, but in the case of oxygen, perspective is obliterated by too confined a view. In this case, geology and chemistry have a great deal to say on evolutionary theory, palaeontology and animal behaviour on medical science. All these fields offer insight into our own lives and deaths. In painting this bigger picture, I have inevitably strayed from my own expertise, and I am indebted to a number of specialists who have spared the time to read and comment on the manuscript (see Acknowledgements).

If an understanding of oxygen's role in life and death requires a multidisciplinary approach, it also offers fresh perspectives on each of these fields. Looking at evolution and health through the prism of oxygen solves some long-standing conundrums. I have already mentioned one specific example: the evolution of two sexes. If we start with the dilemma itself – why did two sexes evolve? – it is difficult to discriminate between one hypothesis and another. We can't even eliminate the possibility that things 'just happened' that way. Thinking about the role of oxygen in ageing may seem to be irrelevant to this problem, but it actually forces us to conclude that two sexes are necessary, and generates a number of predictions. Thinking about life in this way also explains why we cannot extend our lives just by taking antioxidant supplements, and points us to more realistic ways of postponing ageing and the ailments of old age. Oxygen thus acts as a magnifying glass, enabling us to scrutinise life from some unusual angles. That means that this book is about life, death and oxygen, and not just about oxygen.

I have tried to write for a wide audience with little knowledge of science, and I hope I am accessible to anyone prepared to make a little effort. The argument works out over the book as a whole, although this only becomes apparent in the final chapters. Each chapter, however, tells a story of its own, and I have not assumed much prior knowledge from previous chapters. We shall see that life's adaptations to oxygen, which began nearly four billion years ago, are still written in our innermost constitution. We shall see that radiation poisoning, nuclear reactors, Noah's flood, photosynthesis, snowball Earths, giant insects, predatory monsters, food, sex, stress and infectious diseases are all linked by oxygen. We shall see that an oxygen-centic view gives striking insights into the nature of ageing, disease and death. We shall see all this by thinking about how and why oxygen has influenced the evolution of life from the very beginning.

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