A Mitochondria-Based Approach to Metabolic and Brain Health

Disclaimer

As a layman in the field of medicine and health, I've summed up some recent scientific research on the role of mitochondria in human energy and health. I hope you find some of the information useful for counteracting the slow-burning effects of ageing or, if you are young, for optimising the vitality of youth.

I'd like to thank my good friend and highly respected neurosurgeon, Bruce Mathew (https://www.telegraph.co.uk/science/2019/12/21/first-human-head-transplant-may-just-decade-away-former-nhs/), for checking through the draft of this paper, and for his view that it shows the right "direction of travel". His precision, depth of thought and innate professionalism always reflects so well on medicine itself, one of science's greatest enterprises. My respect for all those in medicine, and in the health and social care sector generally, has only deepened since they've been thrown into the frontlines of the covid-19 pandemic. The complexity of the subject-matter they need to grasp, the challenges and threats faced during their careers of serving the cause of public health and their compassion for those who suffer, is deserving of honour.

The reader should take his/her individual medical conditions, dietary issues and lifestyle preferences into account (in consultation with a professional, if considered necessary) when applying some of this information in their lives.

I've focused partly on lowering the risk of cognitive decline during the long ageing process and on some lifestyle and dietary adjustments which may prove useful in the fight against some age-related degenerative diseases.

It's all about maintaining brain and body health through boosting the work which the marvellous mitochondria do inside the body's multitudes of cells.

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Executive Summary

This paper uses secondary research from a review of literature covering topics in cellular biology, the role of mitochondria in human health, metabolism, immunity, the ageing process, cognitive decline in dementia and potential impacts of diet on brain health. It sums up recommendations from experts in these fields, especially in terms of boosting cellular health by enabling the mitochondria within cells to do their vital job in the body with as few metabolic "obstacles" as possible. The argument is that this mitochondria-based approach to metabolism and health may ultimately improve neuroplasticity – the brain's power to adapt to life's stress and ceaseless change.

These recommendations, based on the evidence these experts have accumulated in their studies and careers, are supported by observations on improvements to my own mental and physical health after shifting to the principles of the Banting diet. This diet, along with specific lifestyle adjustments, may be more compatible with the evolved human physiology inherited from our Palaeolithic ancestors than typical Western diets supplied by an excess of industrially modified food.

As brain-centric beings, people can certainly benefit from an increased understanding of how our brains metabolise energy. Since there are widespread incidences of dementia and Alzheimer's Disease in the world today, brain health is a top public health priority. This paper, written by a layman, and acknowledging that the fields of research covered are evolving very rapidly, aims to shed some light on how we can better care for our brains through informed choices about what we eat and how we live.

It's further recommended that we all follow with great interest advances in human understanding of how to slow down ageing and diminish the associated risks of cognitive decline.

In honour of all medical and health care frontline professionals

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1. A Picture of Cellular Health

1.1. What are Cells?

We're built up from cells which, together, make up tissue, while tissue, in turn, makes organs and other bodily material. The good news is that we can take steps to improve the energy production in the trillions of cells making up all the tissues, organs, nerves, blood and bones of our bodies. To improve our health, potentially extend our lifespan and lower the risk of cognitive decline as we age, it's beneficial to keep our cells as energetic and vital as possible, especially our brain cells.

We're only as well as our cells allow us to be, since all living things are made up of cells, the simplest form of life.

Cells have a nucleus, or control centre, where the DNA is stored. And each cell has a plasma membrane to protect it. This outer lining of the cell allows molecules to enter and exit the cell. This fact is important for the flow of energy and information through the body.

There are well over 15 trillion cells in the human body, possibly as many as 30 trillion (30,000,000,000,000). About 10,000 human cells can fit on the head of a pin.[1] And, just to make things even more amazing, if not mind-boggling, there are trillions of atoms within *each* cell.

There's a continuous cellular *renewal* process going on inside our bodies. About a million cells die every second inside us, but billions more are produced from old cell material. One writer estimates that this renewal process represents about 1.2 kg of cells dying and being recycled *each day*.

According to researchers, the body replaces itself with a largely new set of cells about every seven years.

It's when cells don't get replaced, or when too many get damaged, that the effects of ageing start to kick in.

This essay is about giving our little cells all they need to do their job of keeping our vitality in prime condition. By boosting and protecting our cells as best we can, we can optimise our hopes for good health, strong cognition and long life.

[1] "…they are small and squishy and enclosed in a flimsy membrane less than a hundred-thousandth of a millimetre thick." [*Essential Cell Biology*, p. 691]

We'll return quite a few times in this essay to the threat of cognitive decline, but, for the time being, please note that the neurons in our brains are also cells. Crucial to the nervous system, neurons transmit information to other nerves, as well as to our muscles and gland cells. We'll look later at what's known about dementia and Alzheimer's Disease (AD) and see how neurons[2] need the right nutrients and also how their work can be undermined by metabolic stress caused by difficulties in dealing with constant intakes of inappropriate food (along with other contributing factors).

In the section on diet, we'll look at foods which suit the basic human physiology which evolved over a period of more than a million years from our Palaeolithic (old Stone Age) ancestors. As you know, they were hunter-gatherers and they left us with our evolved body structure. Highly processed, mass produced foods can, over time, severely damage the interior workings of our bodies and brains, which, as we know, evolved out in nature long, long ago.

Despite their tiny size, we owe our lives to our cells.

That's because we get most of our energy from cells which process nutrients from food. They carry out the body's functions and keep the body whole. Therefore, we can only be as strong as the food we eat. The way our cells produce energy from food for us is the underlying principle of life. In the words of the sage, "life without energy is dead". Even our bones need energy to maintain their integrity.

It's interesting that water makes up about 70% of a cell's weight, so maybe we can think of a cell as an aqueous, squidgy little entity, but one which is *very* active on our behalf: "… each cell is a chemical factory performing millions of reactions every second." [*Essential Cell Biology*, p. 81]

[2] Most neurons have a cell body, an axon, and dendrites. The cell body contains the nucleus and cytoplasm. The axon extends from the end of the cell body, while the dendrites branch out from the other end. Neurons send signals, or electrical impulses, to one another, with the axons as senders and dendrites as receivers of signals and information. Synapses link the axons and dendrites. The electrical impulses pulse down the cell body and out through the axons. When the synapses are damaged, communication between neurons breaks down. The brain's communications network is incredible: scientists estimate that one neuron may have as many as 7,000 synaptic connections with other neurons. Neurons can even "remodel" or "reset" their synaptic connections depending on what they receive from other neurons. They can strengthen or weaken synaptic connections, break connections with one group of neurons and build new connections with a different group. Sometimes brains generate new neurons in a process called neurogenesis. This remodelling of synaptic connections and neurogenesis is important for learning and memory use. In the brain's housekeeping, microglia protect neurons from damage and clear out foreign substances and cellular debris. This housekeeping takes place during sleep, underlining the importance of sleep. In Alzheimer's disease, many neurons stop functioning, lose connections with other neurons, and die off. Communication between neurons, metabolism, and repair are disrupted in this disease.

The cells have proteins which perform their functions as they work together to create order within us. An example of a protein[3] would be enzymes, which catalyse most of the cell's chemical reactions, enabling it to perform its functions. Most cells contain thousands of enzymes. All the cell's proteins, including enzymes, are like tireless, invisible factory workers, reminding one of the shoemaker's "elves" in the Grimm's fairy tale.

Our lives depend in so many ways on the actions taking place within these humble, but highly productive, units called cells.

Naturally, all this work by cells requires a great deal of energy. As one would expect, cells are skilled at extracting energy and then getting rid of waste products.

Cells are part of nature's unbelievable recycling system, coming from previous cells recycled since the origin of life itself a couple of billions of years ago (*Essential Cell Biology*, p. 609).

In addition to being so productive, cells like to be reproductive. They divide[4] almost at will (as biologist François Jacob famously said: "The dream of every cell is to become two cells"!). The process of cell division happens, for example, after a sperm fertilises an egg to create a new human life.

A cell reproduces by carrying out a programmed set of steps to duplicate itself and then divide into two: "…there is a complex system of regulatory proteins called the cell cycle control system which orders and coordinates these events to ensure they occur in the right sequence." (*Essential Cell Biology*, p. 610). Cells have a beautiful capacity to keep making copies of themselves (unfortunately, this ability applies to bacteria, too).

Each cell carries the DNA molecules and genome of the person, or organism, with all its genetic instructions for making and maintaining the whole organism. With an exception of identical twins, each person has their own unique genome sequence. That's a lot of information packed inside such a small, precious thing. DNA molecules direct the production of RNA molecules which direct the production of proteins. In turn, the proteins carry out the cell's chemical reactions and give the cell its shape.

[3] Proteins are molecules that play many critical roles in the body. They do most of the work in cells. They are essential for the structure, function, and regulation of the body's tissues and organs. They're made up of hundreds of smaller units called amino acids. There are 20 different types of amino acids that can be combined to make a protein. Examples of proteins at work in cells include: antibodies, enzymes and hormones.
[4] Mitosis is when the nucleus divides and cytokinesis is when the cell splits in two (*Essential Cell Biology*, p. 611).

The bottom line, which is comforting to know, is that the cells, with their built-in control centres and DNA information load[5], are programmed for success. They're filled with information as well as energy. Incredible!

Our energy production comes from how our cells produce and distribute energy into the body.

Just like plants use photosynthesis to extract sugars from CO^2, so animals get their sugars from plants they eat and humans get their fuel for life from what they eat in the food chain, which is as ancient as creation itself. And thanks, dear plants, for all that oxygen you keep putting into our air…

Brilliant French scientist, Louis Pasteur, discovered in 1861 that the presence of air accelerates the growth of yeast cells – he'd just unveiled the connection between breathing and metabolism, a connection we see in what's called cell respiration: "Now the oxygen in your breath is being transported to virtually every one of the 15 trillion cells in your body, where it is used to burn glucose in cellular respiration." (Lane, *Power, Sex, Suicide*, p.99).

For those who love aerobics, you'll be glad to hear this process is also known as aerobic metabolism. Our bodies create energy in a combustion ("burning") process which needs oxygen, so that sugars, fats, proteins and carbohydrates can emit energy as a product of the burning. It seems that the energy of living beings is in the form of electron transfers. Oxygen has an affinity for electrons and it accelerates their production along the electron transport chain (ETC).

Now that we've seen some of the amazing properties of cells, it's time to introduce yet another phenomenon about cells. Let's have a drum-roll for the one and only, the super-special mitochondria, living at the heart of our cells….

1.2. The Role of Mitochondria

On average, there are between 300-400 mitochondria in every cell. Mitochondria[6] are the energy factories, powerhouses or batteries of cells. Lane describes them as "flux capacitors" rather than just batteries. Others have described them as tiny generators inside cells, producing the energy cells need.

[5] "Each human cell contains about 2 meters (m) of DNA…Tucking all these material into such a small space is the equivalent of trying to fold 40 km (24 miles) of extremely fine thread into a tennis ball." (*Essential Cell Biology*, p. 178).

[6] The word mitochondria is derived from the Greek words "mitos" (thread) and "chondros" (granules).

Mitochondria use the oxygen we breathe to burn up food we eat to produce that energy that is gradually released: “Electrons and protons are stripped from food, and react with oxygen to provide the energy that we need to live.” (Lane, *Power, Sex, Suicide*, p.207). Lane points out that it is the mother’s egg which passes on mitochondria to children, not the father’s sperm. The zygote, the fertilized egg, contains about 100 000 mitochondria (Lane, *Power, Sex, Suicide*, p.389).

Mitochondria are organelles (sub-units of cells) which nevertheless have their own DNA,[7] and are protected by both an inner and outer membrane. Like cells, they can replicate through division. They have a “shelf life” of between a few days and several weeks. About 10% of our body weight is made up of mitochondria. They’re continuously digested and recycled, with underperforming mitochondria being weeded out: “...new mitochondria are always formed from old mitochondria – they cannot be made from scratch.” (Lane, *Power, Sex, Suicide*, p.288).

The creation of new mitochondria is known as mitochondrial biogenesis.

Mitochondria come in different shapes, but are typically rod-like. They’re mostly found in large numbers in the metabolically active cells within the heart, brain and muscles, with very few, if any, in red blood cells or skin cells.

The actual energy “currency” produced by the mitochondria is the molecule called Adenosine triphosphate (ATP). ATP, which is the energy-carrying molecule in the cells of living beings, is vital – it’s estimated by some experts that every day, we need our own body weight in ATP to fuel all the activities our cells carry out, including nerve impulses, muscle contractions, DNA replication and protein synthesis. The ATP molecule captures chemical energy during the breakdown of food molecules and then releases it to fuel cellular processes.

As one might expect, the two most energy-hungry organs are the heart and brain: “Every day, brain and heart mitochondria have to synthesize around 6kg of ATP.” (Griffiths, *Mitochondria in Health and Disease*, p.17)

[7] In the early 1980s, the mitochondrial genome (mtDNA) was completely sequenced by Fred Sanger and his team at Cambridge. We can sequence the mtDNA for individuals. This could become a big part of a future highly personalised medicine.

How does ATP work? As mentioned, it captures chemical energy obtained from the breakdown of food molecules and then it releases that energy to fuel the processes our busy cells carry out. Cells require chemical energy for such processes as metabolism, transport of substances in and out of membranes and mechanical work like moving muscles. ATP is not a *storage* molecule for chemical energy (like fats and carbohydrates, for example), it's a *shuttle* of energy: "One marvellous molecular machine, the ATP synthase, is a rotating protein motor that spins at 400 revolutions per second. There are tens of thousands of them in each mitochondrion." (Lane, *Power, Sex, Suicide*, p. xxii)

The brain's neurons, too, need lots of energy from the mitochondria. There are tens of thousands of respiratory chains in each mitochondrion, so these dynamic cell "batteries" are well-stocked with what they need!

The energy, once produced, needs to be delivered.

In cognitive decline, the "rails" or "tracks" for delivering the cargo of energy are often compromised. For example, mitochondria move along cytoskeletal tracks called microtubules so that any weakening of the cytoskeleton can undermine the brain's cognition: "…without the microtubule tracks and roads on which to deliver their highly valued mitochondrial goods, energy distribution in neurons is highly compromised." (Griffiths, *Mitochondria in Health and Disease*, p.57) What's encouraging, nonetheless, is that there's the potential for healthy cells, including stem cells, to donate healthy mitochondria to stressed cells.

So, energy production is the main function of mitochondria. As discussed earlier, this is a combustion process we call metabolism: "Metabolic rate is defined as the consumption of oxygen and nutrients. if the metabolic rate falls, then each cell consumes less food and oxygen. And if all the cells in the body consume less oxygen, then the breathing rate, heartbeat, and so forth, can all afford to slow down." (Lane, *Power, Sex, Suicide*, p.234).

Science shows that the mitochondria are the only places in the cell where oxygen is combined with food molecules to keep cells full of energy: "Sunlight energy from plant photosynthesis is being removed from our food, in the form of high-energy electrons. This takes place within mitochondria to generate our own energy." (Griffiths, *Mitochondria in Health and Disease*, p. 30.)

Plants create macro-nutrients from photons from sunlight through photosynthesis and then sunlight charged electrons are released in us when food is broken down in metabolism. It's all part of the great energy cycle, along with photosynthesis: "In this way, sunlight energy is neatly shuttled through food, to be delivered to every single mitochondrion of our being." (Griffiths, *Mitochondria in Health and Disease*, p.32). The mitochondria contain respiratory enzymes to help empower metabolism.

In cellular respiration, then, organic fuels in food are broken down. Electron carriers then take electrons to a group of proteins in the inner membrane of a mitochondrion called the electron transport chain (ETC). As an electron passes through the ETC, the energy it releases is used to pump protons (proton power), which help with the creation, or synthesis, of Adenosine triphosphate (ATP).[8] In sum, the proteins harness the proton power to generate energy in the form of ATP – this process is seen by scientists as being *as fundamental to life as DNA is*.

Bioenergetics is the study of energy production in the mitochondria: "Mitochondria pump protons across a membrane to generate an electric charge with the power, over a few nanometres, of a bolt of lightning." (Lane, *Power, Sex, Suicide*, p.97).

Think about many of the advantages of having healthy mitochondria to produce enough energy for brain and body health: it's worth investing in giving our cells what they need to do their job.

Brain health, for example, gives us better neuroplasticity, which is the key mental ability to adapt to complex changing conditions. The result of such neuroplasticity, when the energy demands of a person can be met, will result in a much lower probability of getting depression, or of suffering from the shrinkage of life and vitality that seems to go along with cognitive decline during ageing.

Individuals with mitochondrial dysfunction can experience a depletion of the brain's energy supply. As their adaptation response falters, depression and/or diseases can set in.

[8] Reactions involving electron transfers are known as oxidation-reduction reactions, or redox reactions. In a redox reaction, a reacting molecule loses electrons and is said to be oxidized, while another molecule gains electrons from the first molecule and is said to be reduced. The flow of electricity in a battery is classified as a redox reaction because electrons flow from a source (which becomes progressively oxidized) to an acceptor (which becomes reduced).

So we need to keep our brains equipped for neuroplasticity by feeding them with the right fuel: "The central nervous system is highly dependent on mitochondria to provide the energy needed to maintain the function of the complex of neurons that make up the brain…people with depression have impaired CNS energy production…" (Griffiths, *Mitochondria in Health and Disease*, p.251).

Furthermore, energy is needed to keep synapses functioning properly: "Mitochondria are transported in large numbers along neuronal cytoskeletal tracks to provide the energy to help build and maintain the integrity of synapses…Slowed neurogenesis (including mitochondrial biogenesis) will mean that a person may not be able to adapt to changing environmental and psychological circumstances." (Griffiths, *Mitochondria in Health and Disease*, p.253).

Mitochondria, then, can help repair neurons and keep the brain "plastic" for adapting to a changing world.

In addition to being energy powerhouses, mitochondria govern apoptosis ("cell suicide") for cells which are damaged beyond repair. If damaged cells aren't "deprogrammed" and recycled in this cellular renewal process I mentioned earlier, they can cause cancerous tumours to grow. Proteins are released to activate enzymes, called the caspases, which dismember the cell from within and then package its contents for reuse later by other cells. Nothing goes to waste in a well-functioning body.

Exercise is an excellent way to regenerate mitochondria. Mitochondrial biogenesis is the process by which mitochondria divide and create new mitochondria from old ones. It's essential to our vitality. (See Section 2.4.2.)

1.3. When Mitochondria are Damaged

Mitochondria, as we've seen, are the energy factory-workers in the cells pumping out energy for us to use. Problems arise in the brain and other organs when mitochondria don't function at their best. For example, much energy is needed for the brain's neurons, or nerve cells. That's because the brain accounts for at least 20% of the body's total energy needs. We'll see later that damaged mitochondria can cause oxidative stress to its neurons.

Please note that excessive use of anti-biotics can harm and kill off mitochondria on a large scale.[9] Some environmental pollutants can adversely affect mitochondria, too. Loss of neuronal mitochondria can increase the risk of depression.

Due to the longer distance travelled by mitochondria in some neurons in the nervous system, when compared to the distance to most other body cells, neurons are more likely to suffer when there are problems with mitochondrial transport. We'll return to this point in the section on Alzheimer's Disease.

As mentioned already, our cells contain a cytoskeleton which helps to maintain cell form and structure, while providing tracks for transport of mitochondria and energy. The tau proteins, discovered by Marc Kirschner in 1975, help to maintain the integrity of the cell's cytoskeleton: "Without tau protein to maintain the cytoskeleton, a neuron will collapse…" (Griffiths, *Mitochondria in Health and Disease*, p.217). In Alzheimer's, for example, the tau proteins become dysfunctional, undermining neuronal cytoskeletons. When cells don't get the energy they need, they can stop working and even die. (There may, of course, be factors other than energy depletion at work, too, some known, and some unknown.)

In sum, energy production by the mitochondria, whereby they produce 90% of the cell's energy, is a foundation of health, necessary for strength, stamina, brain vitality and general well-being: "…synaptic plasticity and neurogenesis both require mitochondria to provide the energy to build and maintain healthy neurons and synapses." (Griffiths, *Mitochondria in Health and Disease*, p. 258).

2. Cognitive Decline

2.1. The Ageing Process

It has been observed that birds tend to live long and healthy lives, without the effects of ageing we tend to see in humans and other mammals like our pets. Parrots have been known to live for over 100 years, while gulls can live for 70 to 80 years without showing signs of ageing.

How do birds live so long with their fast metabolism with such a relatively low risk of disease? Lane believes it's because they leak fewer free-radicals from their mitochondria over the course of their lives (Lane, *Power, Sex, Suicide*, p.394). They often die of muscle wastage, rather than from diseases.

[9] "In addition to overuse of antibiotics by the medical profession, farming adds very high levels of antibiotic residue to ground water. Antibiotics are used as growth promotors in farm animals, but the damage to human mitochondria and environment is vastly underestimated." Griffiths, p.38.

Lane and others think there's a link between the ageing process and numerous degenerative diseases.

And questions of diet and metabolism seem to feature strongly in lots of recent research on how to age while lowering the risk of its associated degenerative diseases.

Two factors seem to come up again and again in these discussions, namely the roles of free radicals and insulin in the body. Let's look at each one in turn and see if the discussion leads to any reasonable conclusions, before moving on to the topic of diet and lifestyle choices.

2.1.1 Free Radicals

In this section, we're not talking about free radicals like Julian Assange but something much smaller and more destructive than the Wikileaks founder, namely unpaired electrons.

How are free radicals produced, what damage can they do and how can we mitigate the risk of their causing damage?

Free radicals have been described as molecules with unpaired electrons whizzing around in our cells like pinballs.

It was Denham Harman who pioneered the study of free radicals in biology: "The free-radical theory of aging was formally proposed by Denham Harman in 1956 and postulates that the inborn process of aging is caused by cumulative oxidative damage to cells by free radicals produced during aerobic respiration. Free radicals are atoms or molecules with single unpaired electrons."[10]

Just a note of caution here is that recent research casts real doubt on how effective anti-oxidants promoted by Harman are. Lane, for example, states there's no evidence after decades of work that anti-oxidants can prolong life, as Harman once said they would. Lane has concluded that anti-oxidants are irrelevant to our efforts to slow down ageing. In other words, they're not the panacea once touted in the health literature. However, this does not negate the importance of Harman's discovery of the damaging health effects of free radicals.

[10] *Encyclopedia of Behavioral Medicine*, 2013 Edition, Ed. Marc D. Gellman, J. Rick Turner - https://link.springer.com/referenceworkentry/10.1007

Substances that can generate free radicals can be found in some food, some medicines, as well as in polluted air and water. The Huntington's Outreach Project for Education at Stanford University lists these substances as fried foods, alcohol, tobacco smoke, pesticides and air pollutants.

Even though free radicals are also the natural by-products of metabolism, we need to try to restrict their production to keep a balance by which cells are not getting extensively damaged. Free radicals are regarded as unstable atoms, looking to make up their number of electrons and therefore reacting quickly with other substances. The chemical processes that result can damage cells and lead eventually to illnesses and accelerated aging.

The free radical theory of aging is supported by a growing body of study. Recent studies on rats, for example, showed significant increases in free radicals as the rats aged. These changes matched up with age-related declines in health.

It’s the mitochondria which are the main source of oxygen-free radicals in body. In cellular respiration, free radicals are released. As indicated already, they’re reactive molecules. They can even attack the DNA in our cells – damage which can be repaired, but which can also become permanent, i.e. leaving behind permanent mutations in the DNA. When the damage reaches a threshold, the cell dies. As cells die, tissues start to degenerate. This steady erosion causes many age-related degenerative diseases and seems to lie behind much of the ageing process itself.

The faster the metabolic rate, the greater is the consumption of oxygen and the higher is the free radical production. The electrons which escape to react with oxygen form the free radicals. That’s because oxygen in the body can split into single atoms with unpaired electrons (oxidising means a tendency to “steal” electrons). These escaped electrons, or single atoms, like humans, prefer to be in pairs. As they seek out other electrons so they can become a pair, they can cause damage to cells on the way. Once free radicals form, they can cause a chain reaction. Which all goes to show that Mr Assange is not the enemy – free radicals are!

As stated already, free radicals can attack parts of the cell, including DNA, proteins, membranes. How effectively our bodies can repair this damage affects how we age. As the body ages, it loses its ability to fight the effects of free radicals. The result is more free radicals, more oxidative stress, and more damage to cells, which leads to degenerative processes, as well as "normal" aging. We'll return to how to deal with free radicals and oxidative stress in Section 3.

2.1.2. Insulin

The second problem area which can exacerbate the ageing process and associated degenerative diseases, apart from free radicals, is when there's an imbalance of insulin.

Insulin is a hormone produced in the pancreas. The pancreas is a gland behind your stomach which creates enzymes to break down the fat, starches, and sugar. It also secretes insulin and other hormones into our bloodstream.

The role of insulin is to help control glucose, or blood sugar, and to regulate metabolism of carbohydrates, fats and protein. It signals the liver, muscles and fat cells when to take in glucose from the blood. Insulin may therefore be described as a key allowing glucose to enter cells throughout the body. When the body has enough energy, insulin signals the liver to take up excess glucose to store as glycogen. Insulin transforms glucose into energy for the whole body, including for the brain and central nervous system.

Insulin is vital to metabolism, and, without it, our bodies would cease to function.

But a lack of insulin can cause diabetes. For example, in type 1 diabetes, the pancreas is no longer able to produce insulin. In type 2 diabetes, by contrast, the pancreas initially produces insulin, but the body's cells are unable to make proper use of it. This is called insulin resistance. Unmanaged diabetes allows glucose to build up in the blood rather than being distributed to cells, or stored.

Blood tests can show whether glucose levels are too high or too low. If there is a problem with insulin, cells might not get enough energy and then they won't work well.

We'll discuss insulin resistance again when looking at Alzheimer's, because "very high insulin levels are a common finding among AD patients" (Berger, *The Alzheimer's Antidote*, p.19).

2.1.3. The Ageing Process in Perspective

Having discussed two underlying factors involved in common degenerative diseases, we can see what conclusions are being reached by some medical researchers. The good news is that mitochondria are very efficient at repair. In each mitochondrion, mitochondrial DNA will have between 5-10 copies of itself, leaving room for some damage to be "undone".

However, ageing results from a gradual, or cumulative, depletion of cells over time: "In time some cells run out of normal mitochondria. When the next call comes to generate more, these cells have little option but to amplify their defective mitochondria clonally, and this is why particular cells are ultimately taken over by defective clones." (Lane, *Power, Sex, Suicide*, p. 439)

As more and more damaged mitochondria are eliminated, the muscles lose tissue – furthering the ageing process: "In most cells, once the ATP levels fall below a particular threshold, the cell inexorably commits itself to apoptosis. Because cells with dysfunctional mitochondria eliminate themselves, it's rare to observe heavy loads of mitochondrial mutations, even in the tissues of elderly people." (Lane, *Power, Sex, Suicide*, p. 440)

While the body has a wonderful ability to recycle cells, make new cells and to repair itself, some cells, unfortunately, are irreplaceable, such as neurons and heart-muscle cells. When they die, the tissue becomes depleted and the body, overall, is placed under greater stress.

Each species of mammal has a maximum life-span potential (MLP), which for humans is currently 120 years. Former heavyweight boxing champion, George Foreman, however, says he's determined to live to 140 years old! Ageing, and its associated diseases, is increasingly seen as caused by a slow degeneration of the quality of our mitochondria. Perhaps one day we will figure out a way to slow down ageing, making it less of a hell for some to go through. Then George Foreman might be able to realise his dream of longevity.

As intimated earlier, Lane and others tie the typical diseases of old age to this underlying process of ageing. They focus on the long-term effects of free radical production. That's because the amount of free radical exposure lowers the threshold for cells to commit apoptosis or cell suicide: "The probability of apoptosis depends on the overall degree of stress, and the ability of the cell to keep meeting its metabolic demands. If it fails to meet its demands, it commits apoptosis. And the likelihood that it will fail depends on the overall metabolic status of the cell, which is calibrated by mitochondrial free-radical leakage as we have seen. The speed at which cells activate the retrograde response and amplify defective populations of mitochondria, leading to an ATP deficit, depends on the underlying rate of free-radical leakage." (Lane, *Power, Sex, Suicide*, p.444). (You'll remember we met Adenosine triphosphate (ATP) earlier, it's the energy-carrying molecule found in the cells of all living things.)

We need, above all, to slow down the rate of free radical leakage from mitochondria "…the degenerative diseases of old age, all of them, could be slowed down, perhaps even eliminated altogether, just by slowing down the rate of free-radical leakage from mitochondria." (Lane, *Power, Sex, Suicide*, p.446)

If too many mitochondria become deficient due to damage caused by free-ranging single electrons, cells can fail, which, in turn, can lead to tissue loss, organ shrinkage and even organ failure.

There can also be chronic inflammation as huge metabolic and cell stress builds up inside the body: "…metabolically active organs, like the brain, heart, and skeletal muscle, are most likely to lose cells by apoptosis." (Lane, *Power, Sex, Suicide*, p.449)

Let's do as the birds do and lower free-radical leakage over our lifetimes, if we can find out how exactly they do it!

2.2. Diseases of Ageing and Cognitive Decline, Including Dementia and Alzheimer's Disease

In recent medical research, defects in mitochondria have been linked to neurodegeneration. This is the progressive loss in function of neurons. As discussed in Section 1, these are cells that make up our brains and nervous system. Damage to certain types of neurons is the root cause of diseases such as Alzheimer's, Parkinson's, Huntington's, and Amyotrophic Lateral Sclerosis (ALS, or Lou Gherig's disease).

We need to look seriously at metabolism to gain a better understanding of ways in which cells can be damaged, triggering various diseases.

For example, Metabolic Syndrome (MetSy) can arise when a body starts to react adversely to over-consumption of starchy and sugary foods with high levels of insulin/blood glucose. Having Metabolic Syndrome, in turn, can increase the risk of developing Type 2 diabetes.

One certainly doesn't want one's body developing insulin resistance. To recall, this condition happens when cells in muscles, fat, and liver start to react to insulin and can't use the glucose from the blood properly for energy. The pancreas then makes more insulin, pushing up blood sugar levels. MetSy, also known as insulin resistance syndrome, includes a group of problems like obesity, high blood pressure, high cholesterol, and type 2 diabetes.

How prevalent is this condition in the West? It's thought by some that it affects as many as 1 in 3 Americans.

Alzheimer's Disease (AD) was classified as a medical condition over a century ago by Dr Alois Alzheimer. Its precursor is Mild Cognitive Impairment (MCI), which can result from excessive daily calorie consumption. It's now thought that mitochondrial issues lie behind many manifestations of this disease: "Mitochondrial dysfunction undoubtedly contributes to common conditions including cancer, Alzheimer's disease, and diabetes." (Lane, *Power, Sex, Suicide*, p.xxiv).[11] New types of mitochondrial therapy are springing up in the light of the increased attention being given to the role of mitochondria in human health, including in brain health.

AD, then, seems to be linked to insulin resistance. Some in the medical field refer to AD as "brain diabetes", seeing evidence of insulin resistance in the brain for conditions ranging from diabetes and obesity to AD itself: "Accordingly, experimental observations are identifying that markers of metabolic dysregulation are also present in AD, the most remarkable being insulin resistance".[12] There is data showing that the brain is an insulin-sensitive organ.

In this school of thought, dementia is seen a metabolic problem requiring metabolic therapy. AD will result from the death of brain cells due to the inability to metabolise glucose. When this happens, brains can become starved of energy as metabolism fails.

[11] It should be noted that Alzheimer's disease is only one specific cause of dementia. More common is multi-infarct dementia, where there is loss of cognitive function from damaged blood vessels in the brain. Dementia is a more generic term, while AD is a specific disease.

[12] "Insulin Resistance in Alzheimer's Disease" Laís S. S. Ferreira,1,2,† Caroline S. Fernandes,1,2,† Marcelo N. N. Vieira,1,3,* and Fernanda G. De Felice1,4,* Published online 2018 Nov 13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6277874

Let's try to illustrate this. Think of neurons in your brain like live wires. Like power lines, they carry a charged electrical impulse. But nerve impulses need to jump across synapses. There are trillions of synapses in each human brain. But in AD, as energy depletes in the brain through failures of metabolism, the axons and dendrites can shrink to conserve energy. During this shrinkage, the neuron's cell body sometimes sucks the axon back in. The synapse is then compromised because the gap to the next neuron is too wide for the nerve impulse to leap cross.

Some of the brain's power lines are then out of service.

AD gradually destroys neurons and their connections, including in parts of the brain involved in memory (such as the entorhinal cortex and hippocampus). As the disease progresses, it can affect the cerebral cortex, the core of the brain responsible for language, reasoning, and social behaviour. Over time, a person with Alzheimer's loses the ability to live and function independently.

What else are researchers saying about this damage to the brain in AD?

Healthy neurons are supported internally by structures called microtubules. In turn, the tau proteins stabilise microtubules. As mentioned early on in this essay, these are the tracks for transport of energy produced in mitochondria.

I often think of the brain as a telephone exchange with lots of messages being routed and re-routed. It's an amazing communications network, with billions of signals being sent every day. That's why the infrastructure of its wiring needs to stay stable so signals from the brain to the body, and back again, can reach their intended destination. It's not just energy that needs to travel smoothly inside the body and its network of cells, it's also information and signals from the brain.

The wires also need power and it is the microtubules which also help to guide nutrients and molecules from the cell body to the axon and dendrites of the neurons.

In AD, however, tau can become detached from microtubules and stick to other tau molecules, forming threads and tangles inside neurons. These tangles can block the neuron's transport system. The synaptic communication between neurons then suffers. Synapses go out of service, as was mentioned.

There have also been suggestions in some literature that AD is accelerated by a faulty blood-brain barrier,[13] which keeps harmful agents out and allows glucose and other nutrients in. In some cases of AD, a malfunctioning blood-brain barrier prevents glucose from reaching the brain, while also preventing the clearing away of toxic elements, causing inflammation: "The research is unambiguous: AD results primarily from a failure of parts of the brain to harness sufficient energy from glucose." (Berger, *The Alzheimer's Antidote*, p.2).

But it seems that it's the free radicals we met earlier that cause the most damage: "As they burn up food using oxygen, the free radicals sparks escape to damage adjacent structures, including the mitochondrial genes themselves, and more distant genes in the cell nucleus….The more seriously compromised cells die, and the steady wastage underpins both ageing and degenerative diseases." (Lane, *Power, Sex, Suicide*, p.5) In this scenario, the metabolism in the brain becomes progressively more dysfunctional. There's degeneration of neurons in the brain's regions responsible for cognition and memory and a weakening of communication/signalling between neurons.

Recall that these free radicals are reactive and can cause mutations to mitochondrial DNA. These mutations, in turn, can bring about diseases.

Lane sees this damage caused by free radicals to be not just the cause of diseases like AD but the basis of ageing itself: "Mitochondria accumulate mutations through use, especially in active tissues, and these gradually undermine the metabolic capacity of the tissue. Ultimately, cells can only boost their failing energy supply by producing more mitochondria. As the supply of mint mitochondria dries up, cells are obliged to clone damaged mitochondria. Cells that amplify seriously damaged mitochondria face an energy crisis …they commit apoptosis…the tissue itself gradually loses mass and function, and the remaining healthy cells are under a greater pressure to meet their demands." (Lane, *Power, Sex, Suicide*, p.475).

Christopher Wanjek, the Bad Medicine columnist for Live Science, defines ageing as a gradual accumulation of free-radical damage, while Lane also measures ageing not in years but in free radical leakage: "...the best way to cure, or at least postpone, the disease of old age is to restrict free-radical leakage from the respiratory chains. This approach has the potential to cure all disease of old age…" (Lane, *Power, Sex, Suicide*, p.476)[14]

[13] The blood–brain barrier (BBB) is a semipermeable border of cells, programmed to select what can cross into the fluid of the all-important central nervous system where neurons reside.

[14] "…lifespan does correlate with the rate of free radical leakage from respiratory chains." (Lane, p.432)

Another problem beyond free radical damage to the system for AD sufferers is that major regions of the brain are unable to properly metabolise glucose. The body's cells become resistant to insulin, as we saw in Section 2: "…very high insulin levels are a common finding among AD patients" (Berger, *The Alzheimer's Antidote*, p.19). It's thought that high levels of insulin prevent the body's other fuel sources, such as fats and ketones, from reaching the bloodstream in sufficient volumes to provide energy for the body, leading to death of cells and neurons. There's a growing shortage of "brain fuel", a struggle within the brain. (Please note that the neurons can only metabolise glucose and ketones).

Usually, years after there's been reduced glucose in the brain, there's a build-up of Beta-Amyloid plaques in AD. This is one of the recognised markers of the disease. These are protein fragments which accumulate in the brain and begin to solidify, interfering with signalling between brain cells.

It's believed that the high level of insulin prevents the removal or lack of clearance of plaques. They're not effectively broken down and removed: "…Beta-Amyloid Plaques are degraded and cleared away by the insulin degrading enzyme (IDE). If insulin levels are elevated it will prioritise clearing away that and allow Beta-Amyloid Plaques to accumulate." (Berger, *The Alzheimer's Antidote*, p. 217)

There are two other contributing factors researchers have highlighted: oxidation and glycation. Let's look briefly at them before moving on to methods of preventing, or lowering the risk of getting, diseases like AD.

When oxidation and glycation happen too quickly, they cause oxidative stress which hampers the repair of cells and tissues within the body.

Oxidation has been defined as a chemical reaction in which there's loss of electrons or gain in the proportion of oxygen, resulting in an increase in oxidation state by a molecule, atom or ion. Haemoglobin is the protein that carries oxygen in the blood, but when haemoglobin becomes sticky with sugar it becomes *glycated* haemoglobin. When there's too much sugar in our blood for too long, its viscosity goes from watery to more syrup-like.

When blood becomes thicker, it doesn't flow as smoothly. This means there'll be poor delivery of oxygen, as well as important nutrients from the blood to the tissues. The heart needs to work harder to pump this thicker blood around the body, sometimes causing higher blood pressure. Hypertension is one of the criteria of metabolic syndrome, a precursor of AD.

Glycation, then, is when blood becomes stickier and syrup-like with too much sugar content. I was astounded to read that even brain cells can become glycated. Glycated cells won't function properly.[15]

Oxidative stress, and the damage it causes, forms part of AD.

Due to a high oxygen consumption, the brain's neurons are especially susceptible to oxidative damage: "…brain mitochondrial glycation and oxidation have combined to do serious damage to neuronal health and cognitive function." (Berger, *The Alzheimer's Antidote*, p.69)

Some studies have connected oxidative stress caused by free radicals to:

- central nervous system diseases, such as Alzheimer's and other dementias
- cardiovascular disease due to clogged arteries
- autoimmune and inflammatory disorders, such as rheumatoid arthritis and cancer
- cataracts and age-related vision decline
- age-related changes in appearance, such as loss of skin elasticity, wrinkles, greying hair, hair loss, and changes in hair texture
- diabetes
- genetic degenerative diseases, such as Huntington's disease or Parkinson's

2.3. Do Anti-Oxidants Effectively Counteract the Free Radicals?

Before we propose ways to reduce the risk of cognitive decline during the ageing process, let's discuss a topic on everyone's lips, namely, is it true that anti-oxidants can combat the destructive work of free radicals? We touched briefly on this topic earlier in the paper.

Anti-oxidants[16] are chemicals that can donate an electron to free radicals, which reduces their reactivity. In the process, anti-oxidants don't become reactive free radicals themselves. So far, so good.

[15] "In fact, glycation of proteins in the kin might contribute to the visible signs of ageing, such as dry and brittle skin, sagging skin and lines and wrinkles." (Berger, *The Alzheimer's Antidote*, p. 66)

[16] Thousands of chemicals can act as antioxidants. Vitamins C, and E, glutathione, beta-carotene, and plant estrogens called phytoestrogens are among the many antioxidants that may cancel out the effects of free radicals. Many foods are rich in antioxidants. Berries, citrus fruits, and many other fruits are rich in vitamin C, while carrots are known for their high beta-carotene content. The soy found in soybeans and some meat substitutes is high in phytoestrogens.

However, recent research shows that no single anti-oxidant can combat the effects of every free radical, given that free radicals have different chemical effects in different areas of the body.

It has also been noted in some literature that anti-oxidants can grab electrons from other molecules, creating some of the instability we see with free radicals, resulting in oxidative stress. Unfortunately, anti-oxidants haven't been the cure or panacea once believed back when free radicals were first discovered.

2.4. Prevention is Better Than Cure

Are there any solutions to mitochondrial diseases? Can we combat our enemy, the free radicals?

There are several mitigating factors that can be powerful in a multi-pronged strategy to counteract ageing and cognitive decline.

2.4.1. Calorie restriction

Lane states tellingly: "…if escaping electrons are responsible for free-radical production, the best way to prevent it would be to minimize the number of electrons passing through any given ETC…Having fewer electrons pass through any given ETC seems to be how the birds do it….we could reduce the number of electrons, which is how caloric restriction works. Caloric restriction is currently the only proven method to extend life span in numerous mammals…To date, calorie restriction is the only mechanism proved to extend the lifespan of mammals like rats and mice." (Lane, *Power, Sex, Suicide*, p.409)

See Section 3.1 on Diet for more details on calorie restriction.

2.4.2. Exercise ("movement is medicine")

It seems that many in the field of medicine have concluded that the best anti-ageing method we know of is regular exercise. It's good for body, mind and spirit. This truth probably adds pleasure to our enjoyment of watching sport and appreciating the athletic achievements of our sporting heroes and heroines.

Exercise has been called the Vitamin M (M for movement or motion)!

Exercise can help maintain insulin sensitivity because it gives glucose somewhere to go. In muscle exercise, for example, the stimulated muscles can soak up glucose like sponges. Muscle cells are loaded with mitochondria.

Exercise stimulates the generation of new mitochondria. It's said that aerobic exercise, for example, can increase the number of mitochondria in muscle cells by up to 50 percent in as little as six weeks (Know, *Mitochondria and the Future of Medicine*, p. 183). Some have spoken of getting 20 minutes of exercise 4 times a week.

Set your mitochondria challenges to grow and generate!

While regular aerobic exercise is anti-ageing in its effects, and can lower the risk of getting metabolic diseases, resistance exercises can help older folks prevent muscle wastage.

Both aerobic and resistance training can produce mitochondrial biogenesis.

For brain health, exercise stimulates signalling molecules that support memory and learning. Exercise is as important for brain health as it is for the body's health, a powerful way to counteract cognitive decline. In addition to boosting overall brain health, exercise can help promote brain plasticity, too: "Exercise has been shown to increase expression of signalling molecules that support memory and learning." (Berger, *The Alzheimer's Antidote*, p.207)

Exercise is vital in lowering the risk of getting dementia: "Researchers have noted an inversely proportional relationship between the amount of physical activity an individual does and their risk for cognitive decline and dementia…the more physical activity someone engages in, the lower the risk for dementia. Exercise also seems to stimulate the growth of new neurons and the formation of new synapses in various regions of the brain…" (see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3549347/)

Health experts warn that it's important not to overdue exercise, but to give the body time to recover so there can be a repletion of nutrition, as well as cell repair. The Bible was spot on to say we all need a day of rest each week. That's because the body has built-in cell renewal and repair processes. The whole of creation has periods of rest, and not just while sleeping, although sleeping remains hugely important to all organisms.

If someone is suffering from the kind of mitochondrial disease we've been talking about in this essay, then exercise becomes even more important. Exercise builds more mitochondria in the cells.

Mitochondria are critical for overall vitality and for maintenance of stem cells. Having increased levels of mitochondria will boost our body's inherent powers of self-renewal. Exercise fights the decline of cells, which can eventually lead to tissue damage and organ malfunction and increased risk of disease: "Mitochondrial dysfunction thus underlies a degenerative cycle that robs humans of the renewal benefits of their own stem cells." (Know, *Mitochondria and the Future of Medicine*, p. 119)

Recall that birds are successful in slowing down free radical leakage and one wonders the role flying plays in this advantage of being a bird! After all, it takes an incredible amount of energy to fly.

Just being outdoors can be energising. The skin, for example, can synthesise Vitamin D from sunlight. It's thought that Vitamin D may protect mitochondria from injury.

2.4.3. "Uncoupling"

It looks like birds live long and healthy lives by uncoupling their ETCs: "…uncoupling is where electron flow is disconnected from ATP production. Instead the proton gradient that is created by the electron flow is dissipated as heat. Uncoupling the proton gradient has profound benefits for slowing the progression of all age-related degenerative diseases and also ageing itself. It could also help us burn more calories and lose weight...by enabling a constant flow of electrons down the respiratory chain, uncoupling restricts the leakage of free radicals." (Lane, *Power, Sex, Suicide*, p. 452).

Salicylic acid 9, or its derivatives, such as aspirin, is a mitochondrial uncoupler. It has been shown to reduce the risk of some degenerative diseases, and even cancers. Aspirin is a mild respiratory "uncoupler".

Let's consider now how to gear up our lifestyle for increased protection of our physical health and brain's vitality.

3. **Lifestyle Health & Vitality**

3.1. Diet

In addition to providing nutrients for physical and mental processes, food is sometimes known as “information” because it interacts with our DNA, providing instructions to regulate processes like inflammation and detoxification.

Diet is the bedrock of our energy production and cellular health.

Diet is also about personal choices. I understand that. It can take weeks, months and even years to adapt one’s lifestyle, or to steer it in a healthier direction.

The following are recommendations gleaned from the literature I studied; please take what’s useful and apply it, and adapt it, as you see fit.

I begin this section by repeating the truth that a calorie-restricted diet has been “proven to reduce free-radical production and reduce mitochondrial damage.” Calorie restriction, that is, is a proven way to slow down ageing.

When a person consumes far more calories than they expend, it results in a corresponding excess of fuel in the body and electrons in the mitochondria. This overabundance of electrons can, in turn, increase the leakage of free radicals.

Calories are essential for human health but the key is consuming the right amount.

What is a calorie? It’s a unit of energy. In nutrition, calories refer to the energy people get from the food and drink they consume, and the energy they use up in activity. Energy and vitality go hand in hand.

But not everybody needs the same number of calories each day. In addition, people have different metabolisms that burn energy at different rates. That’s two reasons right there why diet is personal or individual.

What works for me, and what fits into the way human physiology has evolved for over a million years, is a high fat/low carb/zero sugar diet, championed by the likes of South Africa’s top sports scientist, Professor Tim Noakes. It’s known as the Banting diet. It has helped me to get into better shape (BMI), while boosting mental and physical energy and daily mood management. I am convinced this way of eating, drinking and living will counteract the ageing process.

Zero sugar you say? Yes, but I'm aware that sugar can be more addictive than cocaine, so I understand that this point may be a sensitive issue for many. It took me several weeks to break my sugar addiction. I would never speak lightly of the struggle against human cravings, including the craving for sugar. The good news is that there are healthy, relatively sweet replacements for sugary products. I consume berries, full fat cream, coconut oil, cocoa, unsweetened yoghurt, dark chocolate (85% cocoa) and an occasional teaspoon of honey, snacking on all the above! I have come to love berries, strawberries, raspberries, black berries, blue berries, etc, and they are reported to have neuroprotective properties. Berries are also "low-glycemic" fruits. They could be the number one replacement for sugary products, along with cocoa and coconut. Wimbledon has it so right with its tradition of strawberries and cream!

The high fat/low carb/zero sugar is not a prison diet.

From my reading in preparation for this paper, it seems to me that sugar is a disaster for human health. That's why I aim for zero sugar. No more ice-cream. No more cakes. No less than 85% dark chocolate. No more teaspoons of sugar in tea or coffee. No more sugar-coated, artificially sweetened products from the food industry. No more white bread.

In addition to zero sugar, why do I believe in a low carb diet?

Excessive carbs can drive the processes of glycation and oxidation in the body and brain discussed in Section 2.2. We saw then that brain cells struggle for fuel and ultimately start to degenerate when there's continuous metabolic stress, as those Beta-Amyloid plaques build up and block transmission of nerve impulses. We need lots of nutrients to fuel our brains and bodies and the last thing our bodies need are what's known as "empty calories". Foods high in energy but low in nutritional value provide empty calories, such as those from added sugars, that is, sweeteners added during industrial food processing.

In America, the most common types of added sugars are sucrose and high-fructose corn syrup. These are dietary "baddies".

The following foods and drinks provide most empty calories:

- ice cream
- donuts
- pastries
- cookies
- cakes
- fruit drinks

- some sports and energy drinks
- soda

Water, tea and coffee, by contrast, are great to drink.

Excessive use of alcohol can add empty calories, too. In general, I drink alcohol, mainly beer or wine, in moderation.

Health is partly about what we eat and drink, as well as how much we eat and drink.

We need to balance macro-nutrients and micro-nutrients in our food and drink intake. Dieticians point out that there are three main macro-nutrients: proteins, carbs and fats. Micro-nutrients are vitamins and minerals which help with the production and transport of energy to the body's cells. Vitamins and minerals play a part in repairing and governing cells, too. We want to do our best to increase mitochondria.

A diet high in carbs, but sparse in nutrients, is inflammatory. By contrast, the well-known "Mediterranean" diet is low on the inflammation index. Extra virgin olive oil, for example, is important, and I drizzle it liberally on salads and other foodstuffs. In some metabolic theories of cancer, inflammation is often seen as the first step towards tumour growth. Omega 3 fatty acids can also help to prevent inflammation.

in terms of macro-nutrients, diets which protect mitochondria, and support their biogenesis, would be about 80% fat, 15% protein and 5% carbs. An alternative would be made up of fat 65%, protein 20% and carbs at 15%. I'm not at all "mathematical" about the ratio, but I do aim for a general target of high fat/low carb content in my daily intake of food and drink. It's a diet that really works for me mentally, physically and psychologically. By increasing natural fat content and getting rid of sugary products and high carb foodstuffs, such as starchy vegetables, grains and grain products, I improve the quality of my daily life. Even though it involves sacrifices, cutting out old favourites that might be too starchy or too sugary, like ice-cream, cakes, grain products, potatoes, beans, bananas and apples, there's no shortage of delicious alternative sources of a nutritious way of eating and drinking.

To put this into perspective, think of all the cells that are being renewed in the body every day, including in the brain, heart and major organs, not to mention in muscles and tissue. Take the heart, for example. A heart muscle cell can contain around 6000 mitochondria and "cardiac mitochondria have to synthesize 6 kg of ATP to meet the heart's energy requirements for contraction" every day (Griffiths, *Mitochondria in Health and Disease*, p.177). 95% of that 6kg of ATP for the heart is produced by the mitochondria.

From the proteins, fats and carbs we eat, a brand "new" heart is made about every 30 days!

B vitamins, by the way, are needed for heart health.

Apart from getting these three macro-nutrients from our diet, magnesium, exercise and calorie restriction are all vital for keeping the mitochondria strong.

It's thought that magnesium is probably the most underrated mineral. It's critical to energy production and metabolism and it's estimated it plays a role in 300 biochemical functions in the body.

70% of the developed world could be deficient in magnesium.

Vitamin D, which we can get from sunlight, is considered to be an important regulator of calcium and mitochondria. When there are low levels of Vitamin D in the body, then mitochondria can't utilise calcium effectively, resulting in fatigue.

Vitamin A, too, is a great supplement to health.

What I've learnt in this research boils down to realising the healing properties of a good diet, exercise and stress release. The body is continuously renewing itself and we should do all we can to promote its natural self-renewal processes so we can enjoy the precious gift of health. Why continue to create metabolic and digestive stress for our bodies through consumption of industrially processed, artificially sweetened and starchy foodstuffs that are making a few food companies rich while filling up hospitals, putting health services under strain and complicating and exacerbating the ageing process?

Let's describe in more detail the three main macro-nutrients already mentioned, namely protein, fat and carbohydrate.

3.1.1. Protein

This quote says a lot about why we need protein: “You need to eat enough protein to supply your muscles, organs, and other tissues with raw materials for repair regeneration and overall healthy function, not to mention for making hormones, enzymes and immune system antibodies.” (Berger, *The Alzheimer’s Antidote*, p.126)

Due in part to the way human physiology evolved through our hunter-gatherer ancestors in the Stone Age, proteins are good for us to consume. Check that your meat comes from animals raised on pasture. (We should also check the quality of the meat, as some meat is stuffed with antibiotics due to poor farming practice.) Steaks, chops, roasts, ground meat, game meat, sausages, including animal fat (which is good for the body), liver, kidney, offal, are all valuable sources of protein. Meat is loaded with vitamins and minerals as well as protein. Beef liver is very high in Vitamin A and other vitamins and minerals and is considered one of nature’s most potent “one stop” source of multivitamins. Seafood is also very good for the human body, including all varieties of fin fish and shell fish, canned tuna, salmon, sardines, and mackerel.

It appears that we take in mitochondria from animal protein, too, increasing the number of these vital cell batteries in our bodies! By the way, it’s much healthier to eat pure meat and avoid breaded meats and fillers, as well as starchy, flour-based, deep-fried coverings of meat products.

Another boost for biogenesis of mitochondria, in addition to eating meat, is the supplement BioPQQ. You can buy it over the counter. Cocoa powder, for example, is exceptionally rich in PQQ – in fact, it is four times richer in PQQ than human breast milk. Cocoa is off the charts in goodness, which is why my favourite sweet snack, once my previous addiction to sugar had been broken, is 85% dark chocolate.

Eggs are a super source of protein, too.

3.1.2 Fat

Here’s a statement I read in the research: “We cannot be healthy without fat in our diets…Fat is the most important ammunition in the nutritional arsenal against AD and cognitive impairment...Mainstream nutritionists, dieticians, and medical practitioners now recognize that fat is an essential part of a healthy diet.” (Berger, *The Alzheimer’s Antidote*, p.135-7)

Fat is regarded as a more efficient fuel than carbohydrate. It can help reduce blood pressure. It seems to relieve metabolic stress. In the diet I follow, fat is the most important macro-nutrient of the three: “In general, the higher in fat and lower in carbohydrate and protein a food is, the less it will stimulate insulin.” (Berger, *The Alzheimer’s Antidote*, p. 164)

Here are some sources of fat: avocado, olive oil, salmon, walnuts and coconut oil.

I have a jar of coconut oil on hand on the kitchen table which I eat with a teaspoon for a healthy sweet snack – great brain fuel! You can also add it to tea and coffee for taste. It gives an energy boost, so better not to have some later in the evening. We’re also urged in this diet to use coconut milk in curries and smoothies. Unsweetened coconut flakes are a snack, too, and can be used for “breading” meat cuts and seafood.

Unrefined oils to use are: almond oil, avo oil, extra virgin olive oil, walnut oil, pumpkin seed oil, macadamia oil. We can use full-fat mayonnaise and mustard (unless sweetened) but sweetened tomato sauce should be avoided. We can use vinegar and extra virgin olive oil, which is brilliant as a salad dressing or for drizzling on food that’s a bit dry.

You can get good fat from almonds, avocados, brazil nuts, cashews (although slightly higher in carbs) hazelnuts, macadamia nuts, olives, peanuts (although higher in carbs, like cashews), pecans, pistachios, poultry, pumpkin seeds, seafood, sesame seeds, sunflower seeds and walnuts.

Many dairy products are wonderful sources of fat and protein.

- butter
- heavy cream or whipping cream
- light cream
- cream cheese
- sour cream
- cottage cheese
- all types of cheese
- full fat plain or Greek yoghurt

It is strongly recommended to avoid ice cream and milk shakes, containing lactose or “milk sugar” and to avoid fruit juices which are apparently incredibly sugary.

3.1.3. Carbohydrates

The third macro-nutrient is the carbohydrates. We describing a low-carb diet, not a no-carb diet…so we're looking in this section at non-starchy carbohydrates, including broccoli, spinach, black berries, cucumber, garlic, leeks, chives, artichokes, asparagus, peppers, brussels sprouts, cabbage, carrots, cauliflower, celery, eggplant, fennel, green beans, lettuce, mushrooms, pumpkin, radishes, tomatoes, turnips and yellow squash.

It's advisable in this diet to stick to fruit with lower glycemic load, avoiding dried fruit (with its high concentration of sugar and the water removed) and other fruit high in sugar, such as bananas, grapes, apples, pears and tropical fruits. Freshly squeezed lemon juice is fine, as are *moderate intake* of citrus fruits and stone fruits like peaches, nectarines, plums, cherries, melons.

This approach to diet aims, then, for a roughly 65%-80% fat, 15%-20% protein and 5%-15% carbs ratio for getting your macro-nutrients.

3.1.4. Some Thoughts on Brain Fuel

Omega 3s, found in fatty cold-water fish, organ meats and egg yolks, are generally anti-inflammatory and critical for brain health. DHA (Docosahexaenoic acid) is an omega-3 fatty acid that is a key building block of the brain, accounting for about 40 percent of the fatty acids in the brain's cell membranes.

"Wild-caught fish is the richest source of animal-based omega 3 fats, but you will also find small amounts of these essential fatty acids in beef, lamb, bison, poultry and dairy products." (Berger, *The Alzheimer's Antidote*, p.159). One can also take a fish oil or cod liver oil supplement.

Eggs are one of the brain's best snacks. I keep a stock of boiled eggs in the fridge every week. Seafood is also great for improving brain health: salmon, sardines, mackerel, shrimps, oysters, salmon, mussels, clams.

Oysters and mussels, for example, are loaded with micronutrients: "Oysters, in particular, are an excellent source of highly bioavailable zinc and many older people with compromised cognitive function are deficient in zinc." (Berger, *The Alzheimer's Antidote*, p.163) The body apparently absorbs zinc better from animal and seafood sources than from plants.

The idea is to supply the brain with the nutrients it needs, including vitamins and minerals, especially omega-3 fatty acids, vitamin B12 and zinc: "Low B_{12} levels are an absolute hindrance to strong cognitive function and brain health" (Berger, *The Alzheimer's Antidote*, p.53).

When we switch to a low carb diet, the body uses fats and ketones, with small amounts of glucose for its fuel.

Ketones are described as chemicals made by our liver when there isn't enough insulin in the body to turn sugar (or glucose) into energy. They're produced when insulin levels are very low, by-products of the body breaking down fat, whether stored body fat, or fat in our food. The brain thrives on ketones.

The idea is to dramatically reduce carb intake to lower insulin level and then to boost ketones. Ketones can increase mitochondria production, too. They've been called "clean energy" for the body. The body can run on a combination of different fuels, like a hybrid car, whether glucose, ketones or fat.

Ketones are also produced during periods of low food intake, carbohydrate restrictive diets. Our bodies can then use fat as fuel, with the liver turning fat into ketones, which are then released into the bloodstream and taken up by the brain and other organs. They get shuttled into the mitochondria and used up as fuel.

3.2. Stocking Up

In this approach, it's good to have stocks of:

- ✓ Bacon, lamb, turkey, beef, pork, chicken and seafood
- ✓ Fatty and low-sugar cold meat cuts
- ✓ butter
- ✓ Cheese
- ✓ Eggs
- ✓ Cream
- ✓ Low glycemic vegetables like cucumber, mushrooms
- ✓ Mustard (or unsweetened ketchup)
- ✓ Olive oil
- ✓ Vinegars
- ✓ Canned fish
- ✓ Canned tomatoes
- ✓ Full fat coconut milk

- ✓ Coconut oil
- ✓ Dark chocolate (85% cocoa)
- ✓ Desiccated coconut flakes
- ✓ Nuts and seeds (go easy on cashews and peanuts, as they are slightly higher in carbs)
- ✓ Olive oil
- ✓ Herbs and spices
- ✓ Salt and pepper
- ✓ Beef jerky, etc

Omelettes with low carb veggies, peppers, spinach, mushrooms, onions, etc are delicious as well as nutritious. So are crust-less quiches.

Grass-fed beef is considered by some to be a superfood. In the food cycle, cows harness energy and nutrients from their pasture. Beef liver, in particular, has been described as a superstar food. Pork is also an excellent source of protein and, like beef, is loaded with vitamins and minerals. Chicken, duck liver pate and liver mousse pate are viewed as highly nutritious.

Dairy products should come from grass-fed animals, too. Yellow butter from grass-fed cows is thought to be low carb "gold", just like grass fed beef is. It's awesome brain food!

Meals cooked with a slow-cooker are also recommended….And please use local markets, butchers and local farmer's produce where possible.

Once again, try to avoid sugars and starches – pasta, rice, bread, potatoes, corn, beans, soft fizzy drinks, desserts, pancakes, waffles, muffins, fruit juice, jelly. It's also advised on this diet to leave starchy carbohydrate plant foods like wheat, corn and potatoes.

3.3. Stress Reduction, Rest & Renewal

Here are words from the poem "Desiderata" which meant so much to me as a "troubled youth":

Nurture strength of spirit to shield you in sudden misfortune,

But do not distress yourself with imaginings -

Many fears are borne of fatigue and loneliness.

Beyond a wholesome discipline, be gentle with yourself.

You are a child of the universe.

No less than the trees and the stars, you have a right to be here.

And whether or not it is clear to you,

No doubt the universe is unfolding as it should.

Therefore, be at peace with God, whatever you conceive him to be.

And whatever your labours and aspirations,

in the noisy confusion of life,

Keep peace with your soul.

With all its sham, drudgery, and broken dreams,

it is still a beautiful world.

Be careful. Strive to be happy.

These elegantly-phrased spiritual words capture better than I can ever say how to "let go". A certain amount of stress is needed but in excess it can damage our mental and physical health. It elevates the hormone responsible for the well-known "fight or flight" response. This will provide the body with glucose to survive the threat, giving us a quick burst of energy. However, blood sugar levels may get elevated and, over time, that will push up metabolic stress for the brain and nervous system.

So, we do need to get enough rest during the week, and we need the enjoyment of taking part in activities we find relaxing: "Stress reduction is a key lifestyle factor in reversing the disturbed insulin signalling and other metabolic dysfunctions that underlie AD." (Berger, *The Alzheimer's Antidote*, p.212)

It's been noted in some studies how Type A personalities, who are super-achievers when young, can later suffer from burn-out and even from diseases of cognitive decline, because they never took time to recuperate, recreate, renew during their prime. In later years, they pay dearly for this earlier self-neglect.

A reasonable amount of sleep is needed, in addition to regular rest. Berger has described sleep as a "a mini-cleanse of the brain" (Berger, *The Alzheimer's Antidote*, p.215). Sleep is "Vitamin S" and is important for brain health and cognitive function.

During sleep, the glymphatic system, which is mostly inactive while we're awake, is busy, transporting potentially neurotoxic waste products out of the brain and nervous system to the bloodstream for removal and excretion. There's also a reduction in insulin levels during sleep: "In healthy people, during a long period of sleep, insulin levels will come back to a relatively low baseline." (Berger, *The Alzheimer's Antidote*, p.216-217)

We've all heard about the circadian rhythm of sleep and waking. Melatonin is a hormone that regulates these circadian rhythms. Apparently, getting sufficient exposure to sunlight and fresh air during the day helps the body regulate the circadian cycle.

Just as sleep allows the brain time to clear out waste, so Intermittent Fasting (IT) gives the body time to repair and renew cells. I often skip breakfast these days and perhaps have a spoonful of coconut oil for brain fuel and as an energy boost as I extend the number of hours between evening supper and breakfast.

Clearly, digestion is very energy-intensive. It's been described as a work-out. That's why we sometimes feel sleepy after a heavy meal. It follows that having a break from digestion for a few extra hours saves energy. We already know how much energy the brain and heart and other organs and muscles need. I think it makes perfect sense to give your body a few additional rest periods during the week from digestion: "During a fast, with no food coming into the body, the body is spared the task of channelling resources towards digestion. Instead, it can concentrate its energy on clearing out old cellular debris and repairing damaged tissue – crucial factors for restoring healthy cognition." (Berger, *The Alzheimer's Antidote*, p. 220)

Berger explains why else Intermittent Fasting is beneficial in terms of cellular health: “During fasting, as blood glucose and insulin levels remain low, the body shifts to using fat as its primary fuel source, and upon metabolizing higher amounts of fat, the body produces higher levels of ketones. As we have established, ketones are a super fuel for the brain.” (Berger, *The Alzheimer’s Antidote*, p.219) When the body runs primarily on fat, there are no “wild fluctuations” of blood sugar levels.

Fasting can be therapeutic for the AD sufferer, too. It can reduce oxidative damage to cells.

Back in our evolutionary past, there would have been times of scarcity for our hunter-gatherer ancestors. Intermittent Fasting was probably part of daily life back then.

3.4. The Role of Natural Supplements

3.4.1. A note about Micronutrients

Metabolism of micronutrients is needed for all cellular processes within the body, for example, energy production, neural repair, cognition, and mood state. Important micronutrients include the B-complex vitamins, iron, magnesium and selenium. Micronutrients help with synthesis of neurotransmitters, including dopamine and serotonin, such as B6, B9 (folate), calcium and iron. Vitamins C, E, B2 (riboflavin), B6, D and selenium are all able to reduce oxidative stress.

3.4.2. Magnesium and Zinc

Magnesium and zinc are seen by some health practitioners as having strong anti-depressant effects. It’s thought that a zinc deficiency could be a causal factor for AD (Berger, *The Alzheimer’s Antidote*, p.247). Berger explains that, “Insulin-degrading enzyme, which breaks down amyloid plaques in the brain, requires zinc as a co-factor.”

Good, low-carb sources of zinc include red meat, liver and shellfish (especially oysters).

3.4.3. Coenzyme Q (COQ10)

Co-enzyme Q (COQ10) is a molecule that helps to transport the body’s cellular energy. It’s essential for ATP synthesis. Co-enzyme Q10 “is a critical component of the mitochondrial electron transport system, which is what produces energy in our bodies. It is also a potent antioxidant. With the Alzheimer’s brain struggling to produce energy and under great oxidative stress, CoQ10 could be a powerful adjunct.” (Berger, *The Alzheimer’s Antidote*, p. 248).

CoQ10 can protect against memory loss. It can be taken in the form of ubiquinol. I take it as a natural daily supplement in capsule form. It can be bought over the counter.

3.4.4. Pyrroloquioline Quinone (PQQ)[17]

PQQ also influences mitochondrial biogenesis and neuronal health. It can reduce oxidative stress. Coconut oil and coconut products, parsley, papaya, green peppers and green tea are good sources of PQQ, along with animal foods, including eggs and dairy.

As for COQ10, I take it as a natural daily supplement in capsule form.

3.4.5. Omega-3 fatty acids

Omega-3 fatty acids help maintain your cell membranes, especially in brain cells. They also help with synapses, supporting healthy memory and overall cognition. On top of those benefits, Omega 3 rich oils stimulate anti-inflammatory pathways.

Fatty fish is rated by some as the best source of Omega-3s. I use a daily cod liver oil supplement.

3.4.6. Citicoline (Choline)[18]

Citicoline can help with mitochondria energy production and can support synaptic mitochondria. Citicoline is used for treatment of AD, Parkinson disease, bipolar disorder and other conditions of the brain.

In 1998, the Institute of Medicine recognized choline as an essential nutrient which is vital for brain development. Some research suggests that many people don't get enough of it. Choline supports various bodily functions, including cellular growth and metabolism.

In one study of 2,195 participants aged 70–74 years, those with higher choline levels had better cognitive functioning than those with low choline levels. Another study from 2019 found that insufficient levels of choline, vitamin C, and zinc were associated with weak memory in older men.

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[17] In 1979, the Pyrroloquinoline Quinone (PQQ) compound was discovered as coenzyme of oxidoreductase. In 2003, a research group in Japan suggested that the ingredient has the potential to become a new vitamin. In 2008, BioPQQ® was successfully filed as a New Dietary Ingredient (NDI) with the U.S. Food & Drug Administration (FDA), and Mitsubishi Gas Chemical became the first company to utilize PQQ in food applications. In 2014, BioPQQ® was certified as food ingredient for food application by Japan's MHLW (Ministry of Health, Labour and Welfare). In 2017, the EFSA (European Food Safety Authority) completed a safety evaluation on MGCPQQ®, the European sister brand of BioPQQ®, and the evaluation report was made public. Currently, BioPQQ® is widely used as a food supplement for its various health maintenance functionalities in U.S.A. and Japan, and the ingredient is made available for sale in Europe for the first time.

[18] Citicoline is the ingredient name for a compound that's chemically identical to cytidine-diphosphocholine (CDP-choline). The only difference is that CDP-choline is naturally occurring in humans, and citicoline is the form found in nutritional supplements.

Choline deficiency can contribute to the following health conditions:

- ✓ cardiovascular disease
- ✓ neurological conditions, such as Alzheimer's disease
- ✓ non-alcoholic fatty liver disease
- ✓ neural tube irregularities
- ✓ muscle damage

It can be synthesized from dietary choline. Proteins, such as beef, soybeans, fish, poultry, and eggs are good sources, as are vegetables like broccoli and mushrooms, as well as whole wheat bread, nuts and seeds.

Some multivitamins and dietary supplements, as well as pre-packaged and fortified foods, may contain choline in the form of lecithin.

3.4.7. Curcumin

Curcumin is a natural chemical compound found in the spice turmeric. A turmeric root typically contains about 2-5% of curcumin. It is also known as saffron or yellow ginger.

This quote shows the importance of this natural spice compound: "Curcumin can help protect tau proteins from dysfunction and thus helps maintain the integrity of the cytoskeleton and guard against cytoskeletal degradation…in neurons the cytoskeleton forms the 'railway tracks' which help deliver mitochondria to the synapse – they are also an internal 'scaffold' giving form and structure to a neuron. When tau proteins malfunction, the cytoskeleton collapses, leading to a neuron retreating from a synapse with no track to deliver mitochondrial ATP." (Griffiths, *Mitochondria in Health and Disease*, p219)

3.4.8. Vitamins

Vitamin A plays a role in nerve regeneration, particularly the outgrowth of axons of neurons, the nerve fibres helping to carry nerve impulses. Other brain-critical vitamins and minerals include Vitamin B12 and Zinc.

4. Conclusions

It's possible to counteract the ageing process and lower the risk of undergoing many of the ageing-linked degenerative diseases, including those involving cognitive decline. These four pillars of personal health can help achieve that goal:

- Consumption of a high fat/low carb/zero sugar diet (or proven equally healthy diet)
- Regular exercise
- Getting enough sleep
- Stress reduction through regular rest, renewal and recreation

In my view, these quotes from medical and health experts and writers sum up important truths.

"An exponentially expanding body of research indicates that maintaining inulin sensitivity and keeping blood glucose levels in check are among the most powerful things we can do for our health." (Berger, *The Alzheimer's Antidote*, p.258)

"If we wish to live longer, then, and to rid ourselves of the disease of old age, we will need more mitochondria, but also perhaps a more refined free-radical detection system." (Lane, *Power, Sex, Suicide*, p.460)

As far as I can tell from my reading, the two biggest threats to a long and healthy life seem to be (i) free radicals and (ii) sugar. Many will disagree and prioritise other threats. Each to his or her own….

I've found a diet rich in nutrients for the body and brain is made up of a balance of macro-nutrients and micro-nutrients. My macro-nutrients come from nourishing fats, such as grass-fed meats, wild-caught fish, avocado, nuts and seeds, non-starchy vegetables and salads, as well as, berries, coconut oil, and dairy products including full cream, cheese, butter, but devoid of cereal grains, refined sugars and processed foods. One looks for macro-nutrients and micro-nutrients that stimulate mitochondria health (discussed in Section 1.2-1.3) and don't create high levels of metabolic stress for the body and brain.

Finally, the purpose of improving overall human vitality is to enjoy life to the fullest (John 10:10).

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