



OXIDATIVE STRESS & FREE RADICAL DAMAGE

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Theories of Aging

The National Institute of Health recognizes 20-30 different theories of aging. It is important to realize that all these mechanisms are still classed as theories. Many theories of aging, such as the “Wear and Tear Theory” (simply stated—as body parts are used, they wear out as a car wears out with use) have been abandoned as incorrect. Two theories are favored presently because scientific research has given them support. These are the “Free Radical Theory” and the “Neurohumoral Theory”.

The “Free Radical Theory” states that, with accumulated free radical damage and oxidative stress (explained in more detail below), biochemical and cellular processes begin to do more “incorrect” things as aging damage accumulates. Most free radical damage occurs during times of the most active metabolic turnover. In the human, this would be in early puberty for males and in pre-puberty and early puberty for females. Also during this time, we possess the most physiologic reserve. However, as damage accumulates, our physiologic reserve becomes depleted. Thus, a 20-year-old faced with a trauma or biochemical assault can accommodate and recover faster than an 80-year-old, whose physiologic reserve has been depleted. The “Free Radical Theory” was originally postulated by Denham Harman.

The “Neurohumoral Theory” says that our biochemical processes, especially enzymatic and other hormonal reactions, begin to give incorrect or incomplete messages as we age. This increases over time as we age and damage accumulates. Many experts have pointed out that free radical damage is the cause of this biochemical decline. Thus, this theory may really be viewed as a subset of the “Free Radical Theory”.

As research into aging continues, more and more evidence seems to support the “Free Radical Theory”.

The Cause of Disease

Diseases begin to develop as more and more oxidative stress accumulates in one organ system. When a critical amount of damage occurs, we can identify an actual disease, such as diabetes, atherosclerosis, stroke, cancer, etc. These diseases just mentioned are all “diseases of aging”. Some diseases are the result of simple insult to the organism, such as infections or injury from predators or trauma. Infections and predation are not the result of aging, but involve the risks of living in one’s environment. As the average lifespan of our species has increased, we have seen the appearance of the diseases of aging. These particular diseases occur in the older members of our population and are really not seen with any frequency in younger persons. But, as our average lifespan increased, we began to develop these diseases, all of which are caused by free radical damage. Probably more than any other disease, cancer is a disease of aging. Old lab animals, such as mice and rats, in very controlled environments, mostly all die with cancer.

Inflammation

Presently, there are two hot topics in medical literature regarding the development of disease. One of these involves free radical damage. The other is inflammation. As free radical damage occurs and cells and tissues are damaged, the organism attempts to clear away the damaged cells. In order to do this, various inflammatory pathways are activated. The body’s own cells are sent to the site of damage to “clean up”. These cells release various chemicals that cause inflammation. The inflammation further

destroys and liquefies the damaged tissue so it may be removed. However, inflammation is never restricted only to the damaged cells but also spills over to involve surrounding healthy tissue. Thus, inflammation, although designed for a specific task that is helpful, may actually cause harm itself. In the medical literature, more research is being published regarding the limiting of oxidative stress and inflammation as a way of ultimately protecting functional tissue.

Sources of Free Radical Damage

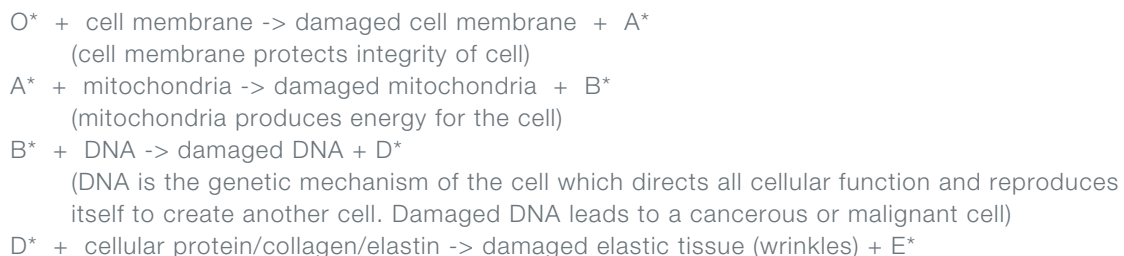
By far, most free radical damage comes from the cell's own metabolism. Our cells take the oxygen inhaled by the lungs and use it in enzymatic reactions to burn fuel (glucose, fat, or even protein) and create energy. Each cell uses its energy to perform its own individual function. Nature did not make us totally efficient in the use of created energy, however. Each cell makes extra energy to ensure it will be able to perform its function. As energy is created, radicals (very high-energy molecules) are created. More are generated than are needed. The extra ones "spin off" into the interior of the cell, combining with whatever structure they strike, damaging that structure. These extra packets of energy are termed "free radicals" because they are not committed to any particular ongoing biochemical reaction. Being of very high energy, they combine with whatever they first touch. Thus, free radical damage can be thought of as a consequence of living and breathing in an oxygen-rich environment.

The skin, being the body's first environmental defense, is also exposed to other sources of free radical damage. Still, the vast majority of each cell's damage comes from its own internal metabolic creation of energy. Other sources of free radical damage to the skin include solar damage, ozone, pollutants, applied substances (for example, some sunscreens) and other toxins. Also, smoking is critical in damaging cells and tissues. Every puff of cigarette smoke contains enough free radicals for a "free radical hit" to every cell of the body.

A condition of "oxidative stress" exists when more free radicals exist than can be neutralized by the various types of antioxidants. Actually, we are always in a state of "oxidative stress" since the number of free radicals is never exactly matched by the number of antioxidants. There are always excess free radicals causing damage and the slow decline of the organism, also known as aging.

The Importance of Antioxidants

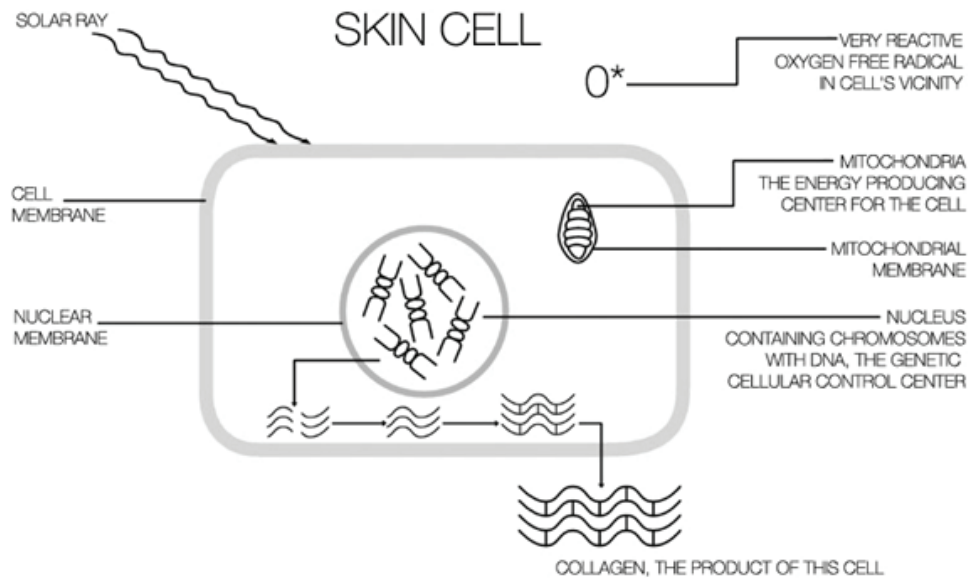
The abbreviated chemical reactions below illustrate the accumulation of free radical damage and oxidative stress. For our first free radical, we'll use the oxygen radical, written with an asterisk (*) indicating it contains very high energy. The O* is of such high energy that it immediately combines with whatever structure it first touches. In combining with this structure, it damages it and, in the process, another free radical is created. This second free radical, being also of very high energy, combines with the first structure it touches. The process continues as shown below.



This process continues forever as cellular structures are damaged by free radicals and more free radicals are created. However, an antioxidant combines with O* at the beginning of this process, neutralizing this entire cascade and preventing all of the ensuing damage. For this reason, antioxidants are crucial to

maintaining cellular function as we age (and, from the time of birth, we are all aging).

Below is a very simple drawing of a cell to illustrate the location of the cellular components mentioned above in the reaction describing damage from oxidative stress. Any of the body's cells could be used to illustrate these general principles, but a skin cell is illustrated here. Remember that a skin cell, being near the surface of the body, is bombarded with additional stressors from the environment that fail to reach other cells far within the organism's interior.



A few additional facts should be noted about the structure of the cell as it pertains to oxidative damage and antioxidants:

1. All membranes are designed to enclose a part of the cell (as mitochondria, nucleus) or the cell itself. Membranes are lipid-soluble (fat-soluble). If they become damaged, they have difficulty protecting their interior structures, as well as letting the right substances in and keeping other substances out of cellular components. Lipid-soluble antioxidants protect these and all other lipid-containing structures. An example of a lipid-soluble antioxidant is Vitamin E, although there are also many other lipid-soluble antioxidants.
2. The interior of cellular structures, including the interior of the cell itself, contain much water. Therefore, aqueous (water-soluble) antioxidants protect these areas. An example of an aqueous antioxidant would be Vitamin C.
3. The DNA portion of the cell in the chromosomes of the nucleus not only directs the cell's function but also directs the reproduction of the cell so that other similar cells can be made. In the case of the example above, the function of this cell is to make collagen. If the DNA is damaged, it may direct the formation of collagen containing "mistakes". Biochemically inaccurate collagen would be unable to function properly; it might have poor elasticity (causing wrinkles) or be unable to bind with other collagen chains (causing wrinkles, loss of resilience, improper scarring).
4. If the mitochondria is damaged, the cell is unable to produce energy as it should. Energy is required for the cell and all of its parts to function. Also, the mitochondria, in producing energy, create radicals as an energy source. Nature designed us to make extra energy and this unused energy begins cellular damage inside the cell's boundaries.
5. Once any free radical (such as solar rays, oxygen free radicals, radicals from smoking, etc.) touches the cell, the cascade of free radical damage begins, as illustrated in the above reactions. Antioxidants can quench free radicals before they touch the cell or inside the cell. It is important to have antioxidant protection at all cellular layers because it is impossible to stop all free radicals at

the surface. Many of them get through the initial skin barrier or come from inside the cell itself via cellular metabolism.

Antioxidants can be ingested (taken orally) or applied topically to the skin. Of ingested antioxidants, only about 1% reach the surface of the skin. To increase antioxidant protection, it is also necessary to apply effective topical antioxidants to the skin.

Good antioxidants for the skin must be of high quality, stability, purity and effectiveness. There are also unique issues in formulating antioxidants to be used topically. Remember that the skin's primary function, simply put, is to keep some substances in and to keep other environmental agents out. This makes the design of topical antioxidants particularly challenging. The skin's own nature works against allowing formulated topical antioxidants to pass to the interior of the cell, where they can do the most good.

The Lifespan Curve

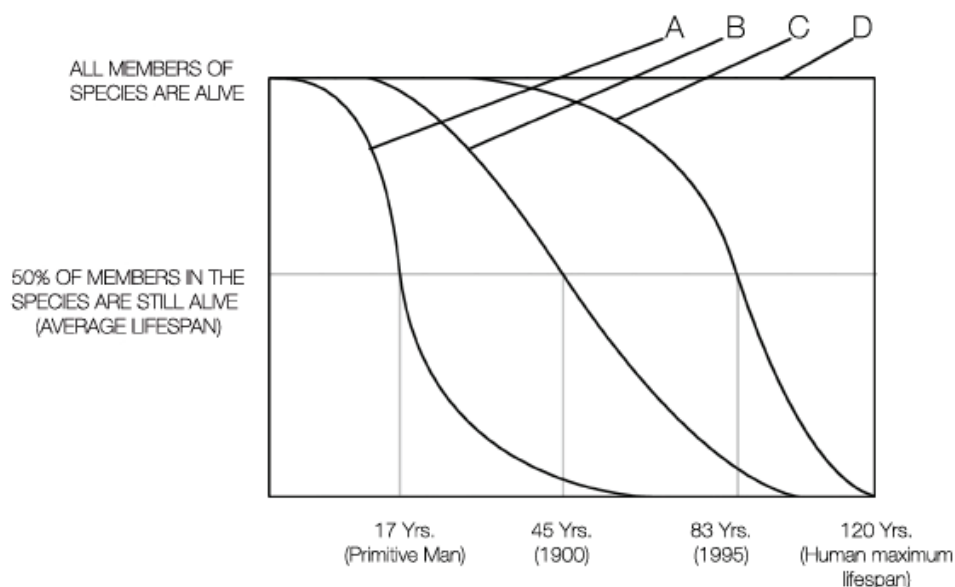
In 1900, the average lifespan was about 45 years. For someone born today, it is about 85. There are some differences between populations in various parts of the world and between males and females. The biggest increase in "average life expectancy" came with the development of sewage systems. As our average lifespan has increased, sweeping social changes have resulted. A life plan and the individual life events for a person expecting to live to be 85 or 90 is much different than that for an individual who will most likely die before 45. Society's challenges are much different as we face an aging population, many of whom will maintain excellent health into their later years.

Each species has a "species-specific maximum lifespan". The maximum lifespan is the age at which the mitochondria inside the organism's cells shut down and stop producing energy. Although there must be some terminal event, individuals reaching the maximum lifespan for their particular species will die. For humans, the maximum lifespan is 120 years. For chimpanzees, it is about 45. For rats, it is about 3 years. For some types of parrots, it is about 105 years. There is some interesting work discussing why some species can live longer than others. Interestingly, there are also species that do not really age. Examples would be the Galapagos tortoise and the rockfish. These species don't seem to get "older"; they simply get bigger. Of course, they are living in the wild so they have a high rate of death from predation and natural events.

Breaking through the species-specific lifespan involves genetic manipulation. In the last few years, Michael Rose at UC Irvine has extended the maximum lifespan of fruit flies and Cynthia Kenyon at UCSF has done the same for Nematode worms. This research has received a tremendous amount of attention because, in the past, we thought the maximum lifespan for a species could not be exceeded.

The Lifespan/Survival Curve below illustrates these principles. This survival curve is for the human species. Each species has a species-specific maximum lifespan, or the longest any member of the species can live before its mitochondria shut down, cellular energy production stops and the organism dies. For humans, the species-specific maximum lifespan is 120 years.

LIFESPAN/SURVIVAL CURVE



Curve A is for Neanderthal Man who, on average, lived about 17 years. This was enough to reach puberty, mate and produce offspring, thus passing on the genetic material of the species. Infant mortality was very high as were death rates from predation, accidents and infections. Nature has designed us, and other species, primarily to live long enough to pass on our DNA so the species continues. After that, it's up to us. In zoos, where predation and natural accidents have mostly been removed, the average lifespan of animals easily doubles immediately.

Sewers and household plumbing helped increase the average lifespan of humans to 45 years about 1900. This is shown by **Curve B** on the graph.

Curve C is our present survival curve. Since 1900, we have developed antibiotics, work has become less hazardous, and other social developments have occurred that prolong life.

Curve D is the "ideal" lifespan curve for man. Here, all members of the species would reach the maximum lifespan of 120 years. In order to do this, disease would have to be eliminated. Sick animals (and humans) die; healthy ones live longer than their ill counterparts. At 120 years, all members of the species die because the mitochondria quit functioning.

Getting a species to Curve D involves a number of sweeping social changes as byproducts of "squaring the lifespan curve". When almost everyone lives to 120, individuals have time for several careers, perhaps several families, may live in a variety of locations, etc. Finding cures for all diseases can alternately be described as curing aging or curing the diseases of aging, such as diabetes, heart disease, stroke, cancer, etc. It also probably involves considerable lifestyle modification, such as dietary changes, not being sedentary, etc.

Getting past Curve D and increasing the maximum lifespan involves genetic manipulation. Michael Rose of UC Irvine has increased the maximum lifespan of fruit flies and Cynthia Kenyon of UCSF has increased the lifespan of Nematode worms. Even though it may seem that work with fruit flies or worms would not apply to humans, the same principles are applicable to all species to some degree. Others have also manipulated maximum lifespan. Much of this work has centered around genetically helping the organisms cells to make more intrinsic antioxidants, such as SOD (superoxide dismutase).

References

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