An Overview: Oxygen: The Molecule that Made the World by Nick Lane.

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Nick Lane has authored a detailed two-volume history on the evolution of life processes, as we know them, and their implications for health, aging and longevity. Lane is an honorary senior research fellow at University College London. The following is a very abbreviated and loose description of his presentation in the first volume.

Lane begins his explication during the early history of the earth when simple single-celled life dominated. As life proliferated there arose an increasing competition for sources of energy to sustain and promulgate life. This led to a diversity of metabolic pathways being developed. One energy source that came to be tapped was sunlight. Tapping the energy in sunlight led to the evolution of photosynthesis. Photosynthesis produced a nasty waste product that most life that existed at the time was not adapted to manage. This waste product was, of course, oxygen, a highly reactive and corrosive chemical.

Organisms that learned to use photosynthesis had a significant energy advantage and multiplied. As they became more numerous the oceans became saturated with their waste to the point that the excess began to "bleed off" into the atmosphere. By this time a large number of bacteria and archaea had become extinct. Those that were left had either adapted to the presence of oxygen or to extreme environments that contained no oxygen. One of the adaptations was the evolution of cellular respiration, which is a metabolic process that could take advantage of oxygen.

These adaptations set the stage for the development of complex cells through a process called endosymbiosis. It is believed that predator cells, probably archaea, engulfed bacteria that had developed cellular respiration. A symbiosis arose between the two cells, because the bacteria were afforded a protected environment, and they released excess energy that was beneficial to the predator cells. Thus, a more complex cell type, eukaryotes, came into existence and contained what is now called an organelle, specifically a mitochondrion. The evolution of mitochondria as cellular energy factories became a critical event that shaped all development that followed.

Most organisms, including humans, are composed of eukaryotic cells that must be protected from excesses of the toxic chemical oxygen. One way this is done is through the use of so-called antioxidants. Lane engages in a long discussion of "antioxidants" and draws three general conclusions: 1) all antioxidants have a wide range of actions; 2) a single action by one of the antioxidants can have many physiological effects other than an antioxidant effect; 3) the precise effects of an antioxidant depend upon the molecules present in its vicinity. He ends by suggesting that there exists the possibility that mega doses of "antioxidants" could be potentially harmful rather than helpful, which may be the reason the body has mechanisms that prevent high concentrations of Vitamin C from building up in the blood regardless of how much we consume. One of the multiple possible actions of "antioxidants" is to provide some protection to cells from oxidative damage and especially damage to DNA.

The need to protect DNA was probably also responsible for the evolution of sexual reproduction. Sex keeps the germ line in good order by recombining DNA from different sources and focusing natural selection on the haploid sex cells. The body is thus subsidiary to the germ line and "designed" to be discarded. Knowledge of this process led to the *soma theory of aging*, which argues that aging is, in general, due to the shifting of resources, at reproductive maturity, from maintenance to reproduction. Under the soma theory, life span is due largely to the balance arrived at between these two biological functions. Lane sees this as good news, for it suggests that we can combat aging by finding ways to shift this balance in favor of longevity. Caloric restriction is one technique that has already been demonstrated to affect this balance by causing more resources to be shifted to maintenance.

Lane next engages in an extensive examination of the *free radical theory of aging* and its connection to metabolic rate. The underlying idea being that the faster the metabolic rate the more oxygen consumed, which in turn leads to more free radical production and damage to cells. On the face of it, this implies that providing more antioxidants should slow down aging. Unfortunately, research has failed to find that antioxidant supplements extend life span. Another problem for the free radical theory is the life spans of birds. Many birds have very high metabolic rates but long life spans. For example, pigeons have metabolic rates similar to rats but live, on average, ten times longer. What lies behind this differential? According to studies on mitochondria, birds' mitochondria are much more oxygen tight and fewer free radicals leak from them, and a greater proportion of their respired oxygen is converted to water. Consequently, they need relatively fewer antioxidants to mop up free radicals. This implies that indeed damage caused by free radicals play a significant role in aging, but antioxidants levels are much less important.

Studies examined by Lane indicate increased resistance to the oxidative stress and resulting damage caused by free radicals can affect life span. Stress resistance is mediated by, in part, levels of stress proteins, e.g., SOD and catalase and by DNA repair enzymes. Lane then discusses the role of caloric restriction on increased stress resistance. Thus, aging appears to be directly affected by the extent of resources committed to prevention and repair of damage, which is programmed genetically but turned up or down, at least in part, by environmental factors. Lane concludes this section by asserting that the primary cause of aging is damage caused by free radicals produced by oxygen respiration in the mitochondria. Mitochondrial DNA has no protective coating of proteins like nuclear DNA and has very rudimentary repair capabilities. Thus, mutation in the mitochondrial DNA is rapid relative to nuclear DNA. Further, DNA in mitochondria is replicated asexually and thus cannot clean out errors by recombination.

If oxidative stress damage to mitochondrial DNA is as serious as it seems then one would expect evolution to have moved mitochondrial DNA to the protected environment of the cell nucleus, which obviously hasn't happened. Lane suggests that the reason this move hasn't taken place is because mitochondrial DNA needs to be passed on to offspring in as pristine a form as possible. Therefore, evolution uses gender to accomplish this task, which requires that mitochondrial DNA be isolated from other DNA. Thus, virtually all

mitochondrial DNA is maternal in origin. Mitochondrial DNA is duplicated, early in development, turned off and encased in eggs where it lies dormant and minimally subject to damage until needed. Thus, the defining difference between males and females is their role or lack of it in the transmission of mitochondrial DNA. In fact, it is suggested that if you want to get an idea about your own longevity potential look at the longevity of your relatives in your maternal lineage.

Lane closes this volume with what he calls the *double-agent theory of aging* by which he means that oxidative stress plays a double role across the life cycle. In youth, oxidative stress arises largely from external triggers such as infectious agents like bacteria. Oxidative stress plays a role in gene activation that in turn initiates an inflammatory response to assist in fighting an infectious agent. When we are older oxidative stress arises largely from internal sources and especially from damage caused by free radical leakage from mitochondria. The cumulative effect is ongoing oxidative stress and chronic inflammation, which eventually results in the degenerative diseases associated with aging. As Lane puts it, "In effect the diseases of old age are the price we pay for the way in which we are set up to handle infections and other forms of stress in our youth." Lane's theory reminds me of a book by Paul W. Ewald titled Plague Times. Ewald too draws a connection between the degenerative diseases of aging and chronic inflammation. The difference is that he attributes chronic inflammation to "stealth infections" rather than to oxidative stress.

How might we overcome the development of chronic inflammatory responses? The best solution would be to engineer our mitochondria to be more like that of birds. Unfortunately, this isn't an immediately realizable goal. There is, however, evidence that long-lived individuals are more likely than not to have a particular mitochondrial gene variation known as Mt5178A, which provides a starting place for potential genetic intervention. However, diet, hormones and activity are avenues that are presently open to intervention. Lane discusses animal research that found the longer lived an animal the lower the levels of highly unsaturated fatty acids found in the mitochondria. It was also found that the older an animal gets the more "unsaturated" it becomes. The level of unsaturated fatty acids in the mitochondria appear to be somewhat subject to diet, but they are not easily manipulated and this approach has limited potential. Research by Bruce Ames and others has shown that carnitine can alter the lipid composition of mitochondrial membranes but also permits more leakage of free radicals. However, when this is used in conjunction with lipoic acid, an effective free radical scavenger, the results seem promising. Diet also has a role to play in hormone regulation, which in turn has a role to play in mitochondrial health. For example, a high glycemic diet that repeatedly causes surges in blood glucose that then stimulates overproduction of insulin is a well-recognized source of stress that contributes to inflammatory responses. Finally, exercise increases the need for energy and stimulates replication of mitochondria, and the healthiest mitochondria replicate the fastest. However, vigorous exercise increases oxygen consumption and thereby increases oxidative stress. Thus, gentle exercise is probably the best, e.g., walking or swimming.

Next, Volume Two in Lane's exploration of mitochondria: Power, Sex, and Suicide.