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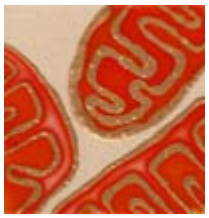
http://www.mitophysiology.org/index.php?lane-n_2005

'**Power, Sex and Suicide: Mitochondria and the Meaning of Life**' by Nick Lane, Oxford University Press, 2005.
£19, $30. http://pages.britishlibrary.net/nick.lane/

Reviewed by Guy C. Brown



Did you think the meaning of life was 42? Think again! According to **Nick Lane**'s new book the deep origin of Power, Sex, Suicide, and, yes, Life is Mitochondria. But this is not a book about mitochondria ruling our present world, but rather about: **the contribution of mitochondria to the history of the evolution of life on earth**. Apparently, without mitochondria, or rather their precursors, there would be no eukaryotes, no multicellular organisms, no big genomes, no sex, and perhaps no life at all. It doesn't sound like much fun. But reading this book is an exhilarating ride through the geography and history of all life on earth, even if much of it is wild speculation.

This book is a sequel to Nick Lane's previous, and excellent 'Oxygen' that described the roles of oxygen in the evolution of life. Both books are 'popular science' but the emphasis here is on the science rather than the popular. Although the writing is brilliant and the narration at times breathless, this will not be a popular birthday present for your precocious nephew unless he is at least an undergraduate, and preferably has a PhD in Evolution, Biochemistry and Mitochondriology.

I liked this book, and loved its bold speculation, but since it proposes serious and ambitious scientific theories, I am going to use this review to critically evaluate those theories.

Nick Lane's main theme is that the endosymbiotic event that gave rise to mitochondria in eukaryotic cells was the key event in the evolution of life. It was an extremely unlikely event that occurred once only after 2 billion years of bacterial evolution, and without this event there would be no eukaryotes, no complex life and no us. The conventional view of eukaryotic origins is that the endosymbiotic event occurred relatively late in the evolution of the eukaryotic cell from an archaean cell, which first lost its cell wall, enabling it to adopt a phagocytic, scavenging way of life, powered by fermentation/glycolysis rather than respiration. This proto-eukaryotic cell, then engulfed an α-proteobacterium, which may at first have lived as an intracellular parasite, as *Rickettsia* still does. But the evolving eukaryotic cell then plugged an adenine nucleotide carrier or equivalent into its passenger and thus gained a source of oxidative phosphorylation. According to Lane, this gradualist theory of eukaryotic cell evolution with a late endosymbiotic/parasitic event is wrong, because new genetic evidence indicates that all currently existing eukaryotes either have mitochondria or had mitochondria and then lost them. Lane, champions the 'hydrogen hypothesis', first suggested by **Bill Martin**. According to this hypothesis the key event was an evolving symbiosis between a methanogen archaean (destined to become the eukaryotic cell) and a hydrogen-evolving purple bacterium (destined to become mitochondria). The methanogen required only hydrogen and CO_2 to live and excreted methane; the purple

bacterium supplied both hydrogen and CO_2 as waste products of its versatile metabolism. So when environmental hydrogen became scarce, due to rising atmospheric oxygen levels, the methanogens cosyed up to the hydrogen-releasing bacterium, a relationship which evolved into an embrace and then an engulfment and transfer of genes.

This scenario seems at least feasible, but there is no positive evidence for it. The closest bacterial relative of mitochondria is not hydrogen-evolving purple bacteria, but rather endo-paracytic *Rickettsia* that can not evolve hydrogen. In the hydrogen hypothesis it is not clear how the hydrogen-evolving bacterium benefits from the relationship with the methanogen, and therefore why it would submit to being slowly engulfed, a process that must have taken many years since the methanogen still had a rigid cell wall.

Lane also outlines **Lynn Margulis**'s idea that the fusion of the bacterial and archaean genomes resulting from the endosymbiotic event, was a revolutionary leap in genetic space, that could not have been achieved by other means. However, it is unclear to me why this could not have been achieved simply by phagocytosis or uptake of genes from dead bacteria.

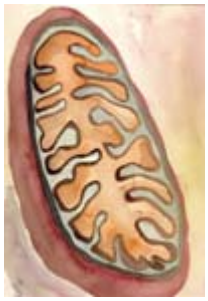
Lane proposes that bacteria could not and can never become large and complex because: (1) their chemiosmotic membrane, from which they derive most of their energy, is in their plasma membrane, and thus their energy production is proportional to their surface area, whereas their energy consumption scales with their volume or mass, so if they become much larger they run out of energy. This argument seems tenuous to me since many bacteria have invaginated inner, bioenergetic membranes that could scale with increasing mass, and there seems no obvious obstacle to the inner membrane pinching off to form internal, bioenergetic vesicles during the hypothetical evolution of a larger bacterial cell. Indeed Lane acknowledges that some bacteria do have external internal bioenergetic membranes. But Lane proposes **(2)** that having internal bioenergetic vesicles is not generally tenable in large bacteria, because of the lack of local genetic control. He argues that the overriding reason that mitochondria have not lost all their genes to the nucleus is the requirement for local genetic control, i.e. each mitochondria needs to regulate the expression level of its own respiratory proteins according to demand (an idea proposed by **John Allen**). Bacteria with internal bioenergetic vesicles, lacking their own genes, would apparently be unable to control these vesicles sufficiently if the cell were of eukaryotic size with extensive internal membranes. However, it is not at all clear to me why local genetic control is required. Local genetic control means that a bioenergetic problem in a single mitochondria would result in a change in a gene expression in that mitochondria alone that corrected the problem. But there is no evidence for such local control. And why would an individual mitochondria need substantially more or less respiratory components than the rest of the mitochondria in a cell? And why is local genetic control restricted to so few genes, and how is a change in expression of the mitochondrial genes to cause a corresponding change in expression of the nuclear genes for the other subunits of oxidative phosphorylation? There is also little point if mitochondria are continually fusing and fissioning within cells as now appears to be the case for most cells. There seems to me no rationale for local genetic control in mitochondria, any more than in other organelles or parts of the cell.

Lane makes a third argument that **(3)** bacteria were and are hampered by the bioenergetic requirement for an outer membrane. So that bacteria could not phagocytose (an apparently very advantageous lifestyle) because of the rigid cell wall/outer membrane. Lane appears to believe that the outer membrane is important to bioenergetic proton coupling because the respiratory chain in the inner membrane pump protons into the space between the membranes, and thus the outer membrane is required to retain the protons resulting in an acidic compartment, which can then drive

protons back through the ATP synthase. This argument is just plain wrong: it is the membrane potential and pH gradient that drives protons through the ATP synthase, not the acidity of the intermembrane space. Bioenergetic coupling per se is not significantly affected by removing the outer membrane (although proteins such as cytochrome *c* may be lost, and the cell become susceptible to osmotic rupture).

Lane bravely speculates that chemiosmosis was there at the beginning of life itself. The conventional view was that life began in a pond of organic soup, which the first life would have fermented. Lane (following **Gunter Wächtershäuser**) suggests that life began in the black smokers or seeps at the bottom of the ocean, where iron, hydrogen and sulphides leek from the reduced earth into the relatively oxidising oceans. Here he suggests iron-sulphide bubbles formed on the ocean floor, consisting of iron sulphide membranes, that could conduct electrons from reduced to oxidising compounds building a pH gradient across the membrane. This is an interesting idea, but lacks details such as the width, permeability, conductivity and catalytic potential of such membranes. Such bubbles might be powered by hydrogen sulphide or sulphides donating electrons through the membranes to hydrogen peroxide or oxygen outside, generating a pH gradient across the membrane. It is less clear what useful work this pH gradient could do prior to the evolution of an ATP synthase to plug into the membrane.

Lane believes that bacterial evolution has always been dominated by the need to reproduce as fast as possible, and that means keeping the cell and genome as small as possible. Lane's central argument is that the incorporation of bacteria/mitochondria into the early eukaryotic cell enabled it to become both very big and very energetic. By acquiring mitochondria within the cell, the cell was enabled to expand in physical size and in genome size; and there was now sufficient energy for new activities such as phagocytosis; and the plasma membrane was freed up to play new roles such as signalling and phagocytosis. Large amounts of space and energy enabled it to accommodate large amounts of DNA, which in turn allowed complexity. Size alone may indeed aid the development of complexity, but Lane is worried by the universal finding that specific metabolic rate declines with size in all animals. Does this decline indicate a constraint on energy metabolism or increased efficiency? This indeed is an important question that is extensively discussed by Lane, but without coming to any firm conclusion.



Having discussed Power, we next turn to Sex. Bacteria swap genes with each other, but they don't indulge in the cell fusion of fertilisation. Lane speculates that early mitochondria may have promoted cell fusion in order to escape from damaged cells, but again there is no real evidence for this. Fusion of two cells at fertilisation may result in competition between the two sets of mitochondrial DNA to populate the new individual. Lane suggests that this competition to replicate mtDNA most rapidly would undermine the energetic function of the mitochondria within the fertilised egg (or fusion of early eukaryotes). So in general one set of mitochondria and their DNA was eliminated by various means, hence we now have maternal inheritance of mtDNA. Lane suggests this is the origin of the two genders; and it provided the opportunity to test the compatibility of the mitochondrial genome with the newly recombined haploid genome of the unfertilised egg. However, it seems to me that an even greater opportunity to test mtDNA function and compatibility with nDNA is presented during the sperm race to fertilise the egg – and yet the fittest sperm mtDNA is simply thrown away when in wins the race and fertilizes the egg. What a waste!

From Sex, we turn to Suicide. There is evidence that some of the proteins/genes (e.g. cytochrome *c* and caspases) currently used to execute apoptosis, were derived from the endosymbiotic α-proteobacterium, and thus were present in the first mitochondria.

Others have suggested that these weapons were used to tame the engulfing cell by killing any cell that attempted to digest its endosymbiotic guests. Its not clear how such death genes could be propagated, and its doubtful that the "apoptotic" genes in bacteria had any apoptotic or toxic function before the endosymbiotic event. But Lane has a different idea: that mitochondrial apoptosis was used to enforce multicellularity at its origin. The evolution of multicellularity was tricky, because most cells in the multicellular organism must give up the right to propagate their genes. Lane suggests that multicellularity was enforced by programming every cell to die if it left its neighbours.

Lane critically reviews the mitochondrial free radical theory of aging according to which mitochondria are the main source and target of the free radicals that cause aging. He believes that mitochondrial oxidant production does indeed underlie aging, and that aging in turn causes most degenerative diseases. But he thinks that anti-oxidants are generally ineffective in preventing aging because mitochondrial free radical production functions to regulate the expression of mitochondrial bioenergetic genes and cellular stress resistance. Instead, he prescribes either mild uncoupling (to lower oxidant production by lowering membrane potential) or increasing mitochondrial number/density (to oxidise the NADH and thus oxidant production at complex I). I believe that the latter prescription would almost certainly be counterproductive in terms of oxidant production. But mitochondrial oxidant production ought to be controllable by anything that regulates electron supply to the respiratory chain, including mitochondrial calcium, malate, malonyl-CoA, pyruvate dehydrogenase complex phosphorylation etc.. Indeed the multitude of ways in which electron supply is regulated suggest to me that mitochondrial leak/uncoupling would not have evolved for the purpose of reducing mitochondrial oxidant production, because it would be so much more efficient to regulate it via electron supply. However, it is not going to be easy to slow aging by limiting electron supply to the respiratory chain (although this is how calorie restriction is suggested to work) because this is inevitably going to limit ATP production when needed. A possible (but difficult) solution is to find alternatives to ubiquinone and flavin, as the partially reduced (semiquinone) forms of these react directly with oxygen, accounting for most mitochondrial oxidant production. Changing the quinone head group will change its redox potential and thus the extent of its reduction in the steady state, and possibility its reactivity with oxygen.

Whatever the deficiencies of Nick Lane's plethora of theories, I can't help being jealous of his audacity, ambition, breadth of knowledge, penetrating reasoning, and writing style. This book is unlikely to be a best seller, but it should be on every mitochondriacs book shelf, if only to get us thinking again about how our mitochondria came to be the way they are.

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