BOOK TITLE:
Transformer: The deep chemistry of life and death

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ISBN:
9781788160544 (hardback, 400 pp; GBP25)
9781782834502 (ebook; GBP21)
9781782839989 (audiobook; GBP20)

PUBLISHER:
Profile Books, London, UK

PUBLISHED:
2022

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HOW TO CITE:
Gevers W. Not afraid to tackle most of the big problems in biology in one book. S Afr J Sci. 2021;118(11/12), Art. #15045. https://doi.org/10.17159/sajs.2022/15045

ARTICLE INCLUDES:
☐ Peer review
☐ Supplementary material

PUBLISHED:
30 November 2022

Not afraid to tackle most of the big problems in biology in one book

It is a truism that the British genius is their wondrous way with words. From Chaucer and Shakespeare, they have led most of the other nations, even the French, in developing and spreading their language which has now become the world's primary intellectual commonspeak. Now we have an English author who is not (yet) a big name in biological science but has written yet another bold and clear book about nothing less than, inter alia, the origin of life, biological energy generation and utilisation, the emergence of species, ageing, cancer and consciousness. And his well-chosen words are worth noting carefully, because the author is very active and well published in many of the fields he covers, is an avid and perceptive reader of the literature, and is clearly a superb teacher, research innovator and communicator.

The author is also bold because he dares to think that the average intelligent citizen can understand the necessary physics, chemistry and biology provided enough trouble is taken to use metaphors and diagrams to make reactions and pathway schemes comprehensible, plus a good deal of repetition, humour and colloquialism to sweeten the pill. The writing in the book is so articulate and the unfolding narrative so ambitious that one is carried along helter-skelter, and the intermittently rough journey is made tolerable by entertaining and alternatively moving and alarming stories about individual scientific contributions by powerful personalities – in each case the actual experiments that revealed the breakthroughs are beautifully described and the generosity or skullduggery revealed. All in all, a first-rate intellectual adventure – even if I fear that not all of the bright ideas may turn out to be strictly true in the long run.

Just as a few top-down causation rebels wish to overturn the 'Modern Synthesis' of random mutation-driven natural selection, Lane would like everybody to turn away from the current genome-centric view of functioning living beings. Instead, he maintains that it is the flow of energy and not the state of the genome that determines whether a cell or an organism lives or dies. The machinery and the physicochemistry of this energy flow operate on time scales that extend from a moment to a lifetime, and it has to work over a huge range of rate requirements – it is composed of enzymes and membranes, metabolites in the form of substrates and products, and it *includes* the contributions of the two kinds of genomes in cells (nuclear and mitochondrial) but that involvement is not the whole story, far from it. Lane rejects the idea of accumulated mutations as the generalised cause of ageing, but rather thinks it is failing or aberrant mitochondrial respiration that resets metabolism on the path to senescence. He thinks the same is true for the origins of cancers. The detail-devil lies in the reasons why respiration is affected, and Lane has some ideas on this but cannot give full chapter and verse.

Two of the three biggest heroes of Lane's story are Sir Hans Krebs (this reviewer's own PhD supervisor) and Dr Otto Warburg, the first for his discovery of his eponymous biochemical cycle, which he thought was the irreversible final common pathway of the respiratory oxidation of most foodstuffs, and the second for his observation of the 'Warburg effect', namely that cancer cells regularly display impaired respiration and instead rapidly break down glucose via glycolysis even when oxygen is freely available, something which normal cells do not do (in turn a prior finding of Louis Pasteur known as the 'Pasteur effect'). Lane uses a wealth of more recent work which has shown that the Krebs Cycle is in fact fully reversible, with alternative enzymes or bypass shuttles being available to overcome the steps in the cycle that Krebs thought were irreversible. In the 'Warburg effect', the cycle in reverse becomes reductive instead of oxidative, biosynthetic instead of catabolic, and a potent engine of the growth of cells, provided that an adequate alternative energy supply is available. The contrasting roles of the two nicotinamide coenzymes, NAD and NADP, are respectively the main cellular oxidising and reducing agents of the forward and reverse cycles. Some Krebs Cycle intermediates are key signalling molecules to set in train multiple pathways affecting growth and inflammation in both cancer and ageing. (In the last-mentioned context, it is curious that Lane does not once mention the well-known operation of the same 'Warburg effect' in activated immune cells such as M1 or pro-inflammatory macrophages, a topic of great current interest in immunology.) The key place of the amino acid glutamine in supporting the growth of cancer cells and in linking their expansion to muscle wasting is, however, emphasised.

The book does not fully recognise, as a potential third great hero of all this biological machinery, Fritz Lipmann, who developed the concept of cellular work of all kinds being done by the splitting of so-called 'high-energy' bonds, meaning that chemical 'free energy' is released that is coupled mechanistically to anabolic reactions (e.g. the biosynthesis of macromolecules like proteins and nucleic acids) or processes (e.g. muscle contraction or ion pumping against gradients in nerve cells). The oxidation of foodstuffs in cells is primarily aimed at forming the predominant 'high-energy' molecule, adenosine triphosphate or ATP. The reason that Lane seems to downgrade Lipmann's emphasis on ATP as the general 'energy currency' of all living cells and organisms, is his (in my view not fully justified) pre-occupation with electricity as the hallmark of life. This leads to *his* choice of third hero as being the maverick scientist Peter Mitchell, whose Nobel Prize-winning work revealed that respiration in mitochondria, driven mostly by the oxidations of the forward Krebs Cycle, actually leads to the formation of ATP through the creation of a powerful 'proton-motive force' (steep proton gradient) as well as electrical potential difference across the mitochondrial membranes. It is the combination of these two factors which causes the positively charged hydrogen ions (protons) to re-enter the inner mitochondrial space, which they can only do via a special membrane-embedded enzyme that makes ATP in profusion, in obligatory coupling to the proton flow. Lane (somewhat disconcertingly, even alarmingly) calculates that the 150–200 millivolts across the 6-nm-thick membrane, as experienced by a molecule present in it, is equivalent to a bolt of lightning!

Lane pursues these ideas (some of which he has also covered extensively in several previous books) to postulate the likely origin of all life in inorganic chemical reactions near deep-water volcanic vents, involving hydrogen and carbon dioxide and sulphur compounds. Protocells formed with partitions that began to be able to develop electrical charge; chemical syntheses of early life-molecules took place without enzymes; primitive RNAs began to code for some of the biosyntheses and to act like enzymes, and gradually the earliest unicellular forms of life appeared. The Krebs Cycle, when it finally worked as a system catalysed by separate enzymes and coenzymes, was all in reverse, a biosynthetic highway. As photosynthesis (also described entertainingly and informatively in a separate chapter by Lane) generated oxygen and this gas accumulated, organisms began to use the forward Krebs Cycle to form ATP but this was largely restricted to the multicellular animals which appeared on earth during and after the 'Cambrian explosion', where some organs needed to do work at high rates and others could concentrate on biosynthesis – so the Cycle became facultative, sometimes going one way and sometimes another, even splitting up sometimes to go in two different directions. A versatile metaphoric traffic circle at the very heart of life. The late Sir Hans would indeed be amazed.

Lane's dominant electrical/biophysical emphasis persists throughout his book (even to a theory of consciousness which questions conventional interpretations of the electro-encephalogram). Thus, he uses the term 'flux capacitator' in one chapter dealing inter alia with fascinating insights into the roles of multiply mutated mitochondrial DNAs in sexual reproduction and possibly in speciation, building on the pioneering work of Douglas Wallace. He devotes much attention to homeostatic mechanisms within the rather dangerous-sounding mitochondrial respiratory environment, involving tight control of the formation of the essential but dangerous 'reactive oxygen species' that are formed mainly by the first complex of the respiratory chain, balanced by the formation of ATP when the chain operates through its full series of components to reduce oxygen to water.

The overall title of the book, the word 'Transformer' (usually defined as a 'device that transfers electric energy from one alternating-current circuit to one or more other circuits, either increasing (stepping up) or reducing (stepping down) the voltage') is not very clearly justified by the author if he meant it to signify the electrical rather than the more general meaning of the term.

This reviewer is convinced of Lane's 'electrical' approach to some degree, but is puzzled by the omission of any mention of alternative or additional mechanisms of energy regulation in living cells. For example, Krebs himself proposed an enzymatic 'flux capacitator' in the form of the equilibrium reaction catalysed in cells by the very active adenylate kinase (myokinase), in which a small fall in ATP concentration results in a large increase in AMP, an allosteric effector that can affect the rates of many key enzymes in glycolysis and the Krebs Cycle. AMP is also a strong activator of a very important protein kinase (AMP-activated protein kinase) with extensive pleiotropic effects on energy metabolism. This kind of selectivity in adducing evidence makes one think that the chemistry/biochemistry of cells and organisms has in the distant past been, and still is, a lot more important in making everything biological happen than Lane gives it credit for.

Nevertheless, all in all, this book is very important because it presents a wealth of ideas coherently drawn together and extending to a wide range of biological phenomena. It is an example of how a full-length exposure in a book of a scientist's 'idea-world' can be more creative and influential than a whole series of journal papers. The book will also be very useful in undergraduate and postgraduate teaching, and in widening the horizons of biologists of all stripes and persuasions. Highly recommended.