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Perspective

ICONOCLASM AND INNOVATION: THE INEVITABLE AND THE APPRECIABLE FACETS OF MURBURN CONCEPT

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My cover-page credited article questioning the highly acclaimed ideas of chemiosmosis (Nobel Prize to Peter Mitchell, 1978) and rotary ATP synthesis (Nobel Prize to Paul Boyer, 1997) was first published for the dissemination of knowledge at *Biomedical Reviews* (2017). Thereafter, in the very same journal (in 2019), my group had called for jettisoning some redundant terminology/ ideas in bioenergetics field, as their impropriety and falsity had been established beyond reasonable doubt. PubMed surveys of leading periodicals of high impact (e.g. *Cell*, *Nature*, & *Science*) and some devoted bioenergetics journals (like *BBA-Bioenergetics, Journal of Bioenergetics and Biomembranes,* & *Mitochondrion*) still show some usage of classical terms like electron transport or respiratory chain, chemiosmosis, proton pump, proton motive force, mitochondrial membrane potential, rotary ATP synthesis, ATP synthase, *etc*. However, murburn pursuits seem to have dampened the further consolidation of the Keilin-Mitchell-Boyer paradigm. Although citations (critical or appreciative) for murburn concept are not forthcoming, some of our articles are well-read by the community. As iconoclasm and innovation are two sides of the same coin of science, it is hoped that murburn concept would soon gain traction with the bioenergetics research community. Towards this purpose, in this review, I succinctly list the salient publications that demonstrate various core aspects of murburn concept. ***Biomed Rev* 2022; 49: 49-52**

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ICONOCLASM, INNOVATION AND PARADIGM SHIFT

In their book on radical thinkers in biology, Harman and Dietrich (1) define a scientific icon as "*the central, explicitly stated organizing assumption in a given discipline, an assumption . . . held and practiced by a substantial majority of researchers*." Therefore, iconoclasm can be defined as a pursuit that challenges the "icon", rendering it refutable. Philosopher Mieke Boon (2) equates iconoclasm with innovation. In his book on big thinkers and scientists of modern times, neuroscientist Gregory Berns (3) points out that entrenched perceptions (the tendency to see novel and non-conforming data along earlier thought lines) and fear of social ostracization as two reasons leading to the consolidation of the inertial mind-sets. He considers winning the Nobel Prize as the recognition of iconoclastic

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pursuits. What if multiple ideas awarded with Nobel Prize are refuted by valid queries/observations and what if the same phenomena are explained with an umbrella of radical ideas that seek us to open our minds, and overlook several decades of aesthetic perceptions in biology? I welcome the reader to murburn concept, a paradigm shifting idea of immeasurable impact in life sciences offering an unprecedented scale of iconoclasm and innovation!

THE BACKDROP AND THE CASE FOR REQUISITION OF REFORMS IN CELLULAR SCIENCES

Human society, like most mass-dynamics of nature, caters and adheres to equations of power. Post the Second World War, Anglo-American forces held the strings of the liberal scientific and intellectual world, as the Communist block was shrouded with secrecy and totalitarianism. Although Mitchell faced some opposition to his ideas in the "OxPhos wars", the recognition with Nobel Prize was not really a big "surprise", as it was along the lines of the earlier Nobel Prize winning "ion-pumping" ideas mooted by Cambridge physiologists (Hodgkin-Huxley-Katz). This recognition to "vectorial membrane proton-pumping (and proton motive force, thereof)" was deemed as the end of quests in the bioenergetics field (although a few individuals did dare to stake their names and reputations even after 1980s). Textbook writers caved in to the winning faction and let go all critical outlooks, and anyone who dared to question the "ion-pumping school" of mainstream bioenergetics line of thought (e.g. Gilbert Ling, Luis Edelmann, etc.) was ostracized.

To me, it was clear by the early 2000s that 1960s-1970s was a period of high intellectual curiosity and output but yet, of low computational and technical prowess (as compared to 2000s). The structure-distribution and process information made available on organelles and proteins at later times were no way compatible with some of the earlier acclaimed theories and it was also evident that the peer pressure to conform along Apollonian mandates was the reason that several classical ideas were still left unquestioned. Further, as a postdoctoral researcher, I had first-hand observed so many intriguing phenomena with redox enzymes that left me convinced that these proteins worked in quite distinct ways. Although respectful of my elders, I always loved the idea to be a rebel with a cause, and this was a nobel (pun intended?) cause indeed! The consequence is: what started with a systematic investigation of heme and flavin protein activities gave rise to the umbrella of ideas called murburn concept. It has now provided deep insights unravelling the physiological function of complex membrane-embedded protein arrays, the role of oxygen in life and also enabled a synthesis of various aspects/theories of cellular function.

MURBURN CONCEPT, A BRIEF AND ESSENTIAL UPDATE

The thesis of murburn concept is based on the fundamental premise that diffusible reactive species (DRS) like superoxide (generated from oxygen) in situ play essential and obligatory roles in maintaining life-order, and this is the real reason why oxygen is needed in such acute time scales. This is when classical purviews DRS it as a toxic and wasteful (undesired) product of metabolism. For an introduction to murburn concept, please refer my group's earlier writings in this journal (4,5). Table 1 lists the key works with unique citations that consolidated the fundamental tenets of murburn concept, and these findings sought us to venture beyond active-site based Michaelis-Menten kinetics and the classical purviews of Marcus ET. (Here, it must not be inferred that I imply any falsity of the two classical treatments above. It is merely stated that there are premises wherein the classical binding criteria no longer hold!)

Table 1. *Unique and key citations for discoveries that consolidated murburn concept.*

№	Fundamental findings that consolidate murburn concept	Year	Ref.
1	mM peroxide does not deactivate heme-enzyme; conversion at active site is critically dependent on reactivity of substrate and its dimensions	2001	(6)
2	selective moiety-transfer could occur outside heme active site; reaction milieu components (ions and redox active molecules) play multiple roles; observed kinetics contingent on various steps	2006	(7)
3	e-transfer mediated outside heme active site; different substrates could have varying pH optima and stoichiometry	2008	(8)
4	rationale for multiphasic profiles with diverse substrates and substrate-dependent inhibitions	2010	(9)
5	flavo-enzyme generates DRS and also modulates/depletes DRS	2010	(10)
6	complex aspects of heme enzyme catalysed reactions like thermodynamic pull, dependence on heme-site concentration	2016	(11)
7	stochastic inter-molecular e-transfers via DRS	2016	(12)
8	stochastic intra-molecular e-transfers via DRS	2022	(13)

Over time, we have applied murburn concept to elucidate the phenomenology (cause-consequence scheme of events) in various scenarios, which are listed in another article within this issue (14). To gauge the impact of our work on bioenergetics [post the publication of some landmark critiques on the classical bioenergetics paradigm (15), and after the dissemination of our critical article seeking the discontinuation of some terminologies (5)], the data in Table 2 are presented, which can be interpreted in two ways: (A) in spite of clear pointers, some members of the research community and publication industry have continued along lines demonstrated to be redundant. OR (B) given the critical pointers, significant number of researchers have minimized their usage and application of the KMB (Keilin-Mitchell-Boyer) perspectives.

In respiratory and photosynthetic bioenergetics, I urge the members of research community that other terms like: Q cycle (quinone cycle), Z-scheme, Kok Joliot cycle, water splitting complex, oxygen evolving complex, electron bifurcation at heme, *etc*. must also be discarded, as they are no more relevant (and as they were intangible and untenable, originally). In other cellular functions (protein-protein electron transfer, retinal visual cycle, etc.), the ideas brought forth by murburn concept must be incorporated. Most importantly, the idea that redox enzymes (using protons) work fully reversibly in physiology must be closely scrutinized and the notion that membrane pump ions must be revisited. In toto, such iconoclastic pursuits would inevitably mandate the appreciation and embracement of murburn concept as a fundamental guiding principle of routine activities of life. I must also caution the inertial ones in the community that continuing to use redundant terminology shows that one is either outdated or cognitively dissonant (i.e., immoral). A researcher must owe allegiance to truth first, then to journal impact factors, citation indices, etc., and for doing science, it is imperative that one must open oneself to alien thinking (16).

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Table 2. *PubMed hits for classical bioenergetics description terms, as published in six journals during the three year period of 2020-2022. Keywords are explained in footnotes. The data may be compared to Tables 1 and 3 of our 2019 review in this journal (5).*

№	Terminology	Cell	Nature	Science	BBA-Bioenerg	J. Bioen. Biomemb	Mitochondrion
1	ETC / RC	0 / 6	2 / 11	2 / 10	16 / 36	0 / 0	8 / 12
2	Chemiosmosis	0	0	0	0	0	0
3	PP / *pmf*	0 / 1	1 / 0	2 / 0	14 / 6	1 / 0	5 / 4
4	MMP	2	1	0	4	1	11
5	RAS / ATPS	0 / 0	0 / 1	0 / 0	1 / 10	0 / 1	0 / 0

1. electron transport or transfer chain (ETC) / respiratory chain (RC)
2. chemiosmosis or chemiosmotic
3. mitochondrial proton pump (PP) / proton motive force (pmf)
4. mitochondrial membrane potential (MMP)
5. rotary ATP synthesis (RAS) / ATP synthase (ATPS)

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