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COMMENTARY

A Clinician's Commentary: Mitochondria and Revolution

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INTRODUCTION

Clinicians embrace revolutions that empower them. Empowerment for us involves having the means to prevent disease, reduce suffering, and improve health. Popular perceptions aside, revolutions do not occur precipitously. Many events interact, often over a prolonged time period, to produce the specific changes in thinking and consequent behaviors that we label "revolution" (Table I).

At the end of the 19th century the germ theory of disease presented Western medicine with such a revolution. From Lady Montagu's 1718 observations and applications to her own children of "variolation" through the works of Jenner, Schwann, Cagniard-Latour, Henle, Semmelweis, Pasteur, Lister, and Koch, 160 years tumbled by before the germ theory of disease began its growth to wide acceptance. This 160-year span of time is eerily similar to the first description in 1850 of what we now call mitochondria and this 2011 theme issue of *Pharmaceutical Research*.

Until very recently, the basic approaches to drug discovery, development, and therapeutics remained unchanged. Our traditions of investigation, combined with new technologies and increased cross-disciplinary interactions, led to our rapidly evolving new disciplines of proteomics, metabolomics, genomics, bioinformatics and integrative genomics, nucleic acids research, and most recently epigenetics. All contribute to the evolutionary changes in thinking about living systems. None of these new disciplines unto themselves represents a revolutionary change. Significant—revolutionary—change requires major new ways of thinking about intra-cellular function and multi-cellular systems. The discovery and growing understanding of mitochondria set the stage for drastic changes in perception and thinking about eukaryotic biology that now finally rise to the level of a recognizable revolution.

THE STAGE IS SET

The 19th century descriptions (Rudolph Albert von Kolliker and Richard Altmann), followed by subsequent study of these organelles, opened the doors to this biologic revolution. Slowly, descriptions of mitochondrial structure and function accumulated, until in 1962 an endocrinologist at the Karolinska Institute, Rolf Luft, described the first patient whose illness was based on mitochondrial dysfunction (1). Ten years later, Lewis Thomas wrote about the uniqueness of mitochondria in contrast to other parts of a cell in terms of their membranes, their DNA, their RNA, their ribosomes, their use of oxygen, their putative origins (endosymbiotic theory), and their existence in all forms of

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Table I Mitochondrial Diseases: Some Promising Therapeutics

Decreasing ROS and enhancing mitochondrial function	Examples include administration of CoQ10, idebenone, L-carnitine, and newer quinone-based antioxidants such as alpha-tocotrienol quinone and other NQ01 modulators.
Improving mitochondrial metabolic function	Examples include administration of L-carnitine, thiamine, riboflavin, creatine, and dietary nitrates (Nair, et al. Cell Metabolism, 2011).
Elimination of toxins	Use of DCA to decrease lactic acid accumulations; use of copper-histadine compounds for thymadine accumulations
Elimination of abnormal/mutant genes	Development and use of gene silencing molecules that cross both mitochondrial membranes and bind to DNA such as oligonucleotides/si RNA's; zinc fingers; cytoplasmic transfer during IVF (Craven et al. Nature, 2010)

Schon *et al.* Therapeutic prospects for mitochondrial disease. Trends in Molecular Medicine. 2010; **16**; 6: 268–276

Shrader *et al.* Alpha-tocotrienol quinone modulates oxidative stress response and the biochemistry of aging. Bioorganic & Medicinal Chemistry Letters. 15 June 2011; **21**; 12; 3693–3698

eukaryotic life. In reflecting on mitochondria he concluded: "We seem to be living through the biologic revolution… without being…much disturbed by it" (2).

In 2006 the first textbook of Mitochondrial Medicine, edited by DiMauro, Schon, and Hirano, became available (3). By 2010 over 1,600 gene products essential to a broad array of cellular maintenance and specialized functions had been identified in mammalian mitochondria. Six maintenance functions include carrying and transport, the morphology and inheritance of organelles, nucleic acid metabolism, protein import and sorting, protein translation and stability, and regulation of stress responses. Six specialized functions include apoptosis, amino acid and nitrogen metabolism, intermediate metabolism, lipid metabolism, respiratory chain and oxidative phosphorylation, and signal transduction (4).

Mitochondria are truly extraordinary organelles. They actively move throughout cells (note that a single adult human sciatic nerve cell can be over one meter in length) and have been observed to leave cells. Mitochondria can repair one another through recombination, form tubular networks within cells, divide by binary fission, and seemingly interact with other intracellular structures forming mitochondrial associated membranes (MAM), most particularly with the endoplasmic reticulum (5).

More than 200 changes (point mutations, deletions, duplications) of mitochondrial DNA alone are known to generate a wide array of multi-system diseases. Most are rare. Based on mitochondrial DNA and nuclear DNA mutations, there are at least 50 named diseases. As the field of interest in nuclear and mitochondrial DNA-based disorders grew, most medical practitioners as well as most of the pharmaceutical research community paid scant attention. In 2008 no storm of interest was created by Patrick Chinnery group's fetal cord blood study revealing that at least 1 in 200 individuals harbor pathogenic mitochondrial DNA mutations (6). Even the 2010 collaborative publication by the Mary Herbert and Douglass Turnbull groups describing their approach to preventing the transmission of human mitochondrial disease generated relatively little notice (7). After all, how many cases of Friedreich's Ataxia or Leber's Hereditary Optic Atrophy (LHON) or Myoclonic Epilepsy with Ragged Red Fibers (MERRF) does the average clinician see, no less treat, in a lifetime?

THE REVOLUTION EVOLVES

Now in the early years of the 21st century mitochondria are breaking out onto the world stage. Clinical groups and laboratories from around the planet publish about the role of mitochondria in the cancers, immune system dysfunction and inflammation (8), endocrine dysfunctions such as diabetes, Huntington's Disease, the different forms of Parkinson's Disease, Amyotrophic Lateral Sclerosis, psychiatric disorders, even aging itself! This "horizontal flow" of the relevance of mitochondria to health, illnesses, and aging feels uncomfortable in our traditional conceptual framework, established hundreds of years ago, that grew out of observations of form and function, anatomic dissections, and microscopic examinations of tissues, cells, and cellular structure. We continue to treat people in Western medicine by focusing on anatomy, organs, and organ systems. Our healthcare system and its institutions remain organized around specialty constructs such as dermatology, pulmonology, endocrinology, cardiology, or the constructs of disease clusters such as hematology/oncology and rheumatology. Given what we are learning about mitochondria and the questions they raise about cellular and organ function, how on earth does our traditional way of thinking and organizing treatment continue to make any sense? Our current ways of thinking about biologic systems and how they function need to be examined.

The current wide-spread clinical and research realities that spend huge amounts of money as well as lifetimes continuing to only bear down on the details (for example, studies in membrane transport, discovering new deletions that produce tRNA errors, describing more micro RNAs

and their roles in regulating intracellular processes) do add to information, and are therefore "evolutionary" endeavors, but are missing the essence of this revolution. You can describe in exquisite detail the outside, the inside, and the mechanics of a piano. But to understand the music that can be produced by it, such as a Bach Fugue, you need information about the performer, the energy applied through the performer, the notes played, the rhythm, the timing, the phrasing. Similarly, we can study the forest for its trees, undergrowth, lichens, moss, soil composition, and streams, but that is only part of the reality that keeps any particular forest healthy and growing.

THE REVOLUTION

Given the past 160 years of growing awareness of mitochondria, where's the revolution and what is it? The revolution does focus us on the generally unasked question: how does it all work? How do we understand not only energy flow as in oxidative phosphorylation, but energy as it allows proteins, the many forms of RNA, other molecules to do their jobs in appropriate *and timely* fashion, to open and close nuclear pores and ion channels at the most optimal moments for cellular function. Understanding the flow of energy in these complex micro-universes is essential, but not sufficient. The other critical piece is timing. What determines the timing: what regulates biologic time? The wrong timing makes a musical composition unpleasant, even if all the notes are played exactly correctly. The wrong timing for cycles of moisture and temperature can influence whether a plant thrives, is disease resistant, or dies. The timing of inorganic or organic chemical interactions similarly can produce varied results, ranging from ideal efficiency to lack of success.

The revolution imposed on us by mitochondria now has us re-asking ourselves what energizes and orchestrates the complex "universes" within each cell, no less cell-to-cell communication and collaboration. We cannot be sure where any revolution will take us. But two individuals, and their collaborators, direct us to some intriguing possibilities. Douglas Wallace, with a Ph.D. in microbiology and human genetics, has a long and respected history in the field of mitochondrial research and academia. He now focuses on the role of mitochondrial energy in health and disease. An articulate, imaginative, and gifted synthesizer, Wallace speaks of the "organ-specific compartmentalization of medicine" and our almost exclusive focus on Mendelian (nuclear) genetics, while we give scant attention to the complexity (rapid mutation, heteroplasmy, and threshold effects) of mitochondrial genetics. He calls for the generation of "a new paradigm" because the Mendelian one fails "to direct us toward solutions for the common age-related diseases." In his reflections on bioenergetics, he states "we must understand how energy flows….how this energy flow increases biological information…" (9,10).

Guy Miller, an M.D. with a Ph.D. in chemistry, left academic medicine to develop drugs targeting energy metabolism. He started his first of four companies using DARPA funding to target brain injury but now focuses on mitochondrial diseases. His current team, using R&D tools more commonplace in electrical engineering and physical chemistry, builds drugs that target the cellular redox state and modulate metabolic control. Their first drug candidates represent a new class of therapeutic agents that he calls biochemical information transfer and sensing compounds (D-BITS). Their lead compound, EPI-743, modulates a previously unappreciated cytosolic redox system critical to mitochondrial function and the regulation of biochemical time. His research group systematically uses D-BITS as probe compounds to uncover how cellular metabolism is regulated. Their goal is to exploit this information to develop therapeutic agents that target not only rare mitochondrial diseases but even more broadly the many diseases of aging (see technology section of www.edisonpharma.com).

A CLINICIAN'S PERSPECTIVE ON THE MITOCHONDRIAL REVOLUTION

My patients suffer from complex chronic illnesses. Their burdens include pain, diminished energy, economic, as well as psychosocial challenges. As occupiers of the land of chronic diseases, their hopefulness tends to focus on maintaining, at some level, an engagement with life. Current medical knowledge and skills do help reduce their suffering. Our patients remain open to the possibilities of any new treatments that could restore energy, reduce pain, and improve their functioning. Yet, clinicians remain frustrated by our current therapeutic limitations.

All patients are intrigued by anything that promises a more personal management of their disease. Those exposed to Star Trek episodes or re-runs would love to see hand-held electronic diagnostic devices that would lead directly to targeted successful treatment. Such a story grabs their attention, but in general they show no interest in the passions of scientists who study metabolism, transporters and enzymes, nanosystems, new formulations of biologic activity, new approaches to drug targeting. Their attention is only grabbed when news stories seem to promise improved control over, or out-right cures, of disease states.

Waldman and Terzic wrote in 2008 of "the development of molecular targets for individualized therapies" as one path forward in 21st century medicine (11). This is possible only if the community of scientists opens itself up to the possibilities and risks of broadening its thinking. And this is exactly where mitochondria have led us: to dramatically re-

consider how we think about ourselves and other eukaryotes. Re-phrasing Lewis Thomas's 1972 comment (2), we must *allow ourselves to be much disturbed by this revolution in biology*. Doing so will open very new approaches to drug development and therapeutics.

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