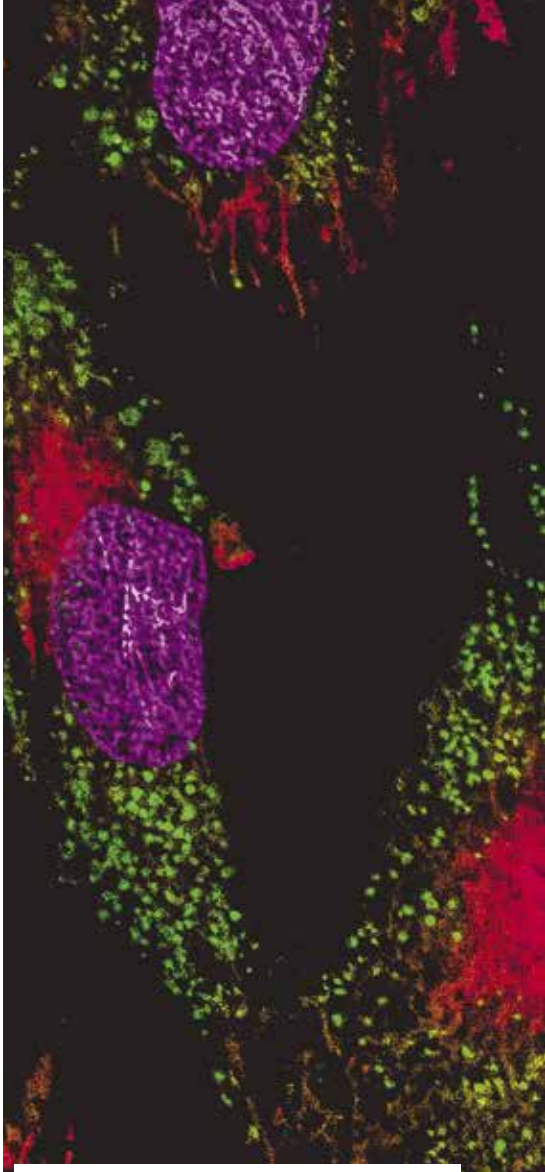
The Cell Danger Response: a new paradigm for understanding chronic disease?



When danger threatens, mitochondria alter their cellular metabolism to shield the cell from further injury – triggering a cascade of responses affecting methylation, energy production and more. **GILIAN CROWTHER**, Director of Research for the Academy of Nutritional Medicine, explains how the ground-breaking research of Prof Robert Naviaux has unlocked a new understanding of mitochondria's pivotal role in chronic disease.

Dr Robert Naviaux, MD, PhD, who runs the Mitochondrial and Metabolic Disease Centre at the University of California, first introduced the concept of the Cell Danger Response in an article in *Mitochondrion* in 2013: "Metabolic features of the Cell Danger Response". (1)

Dr Naviaux is a Professor of Genetics, in the Departments of Medicine, Paediatrics, and Pathology. He directs a core laboratory for metabolomics at UC San Diego. He is an internationally known expert in human genetics, inborn errors of metabolism, metabolomics, and mitochondrial medicine. He is the discoverer of the cause of Alpers syndrome – the oldest Mendelian form of mitochondrial disease – and the developer of the first DNA test to diagnose it

Dr Naviaux says: "The cell danger response (CDR) is the evolutionarily-conserved metabolic response that protects cells and hosts from harm. It is triggered by encounters with chemical, physical, or biological threats that exceed the cellular capacity for homeostasis". This is a response activated when a cell encounters a threat that could injure or kill it.

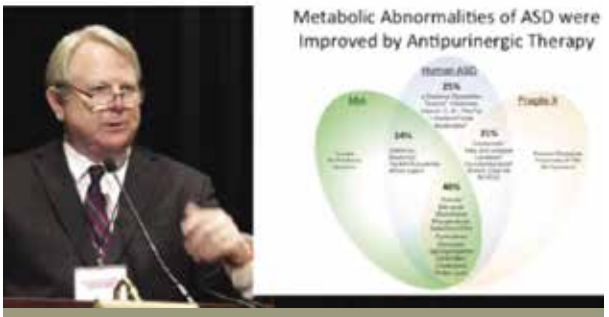
Threats that he cites include:

- **Biological** – viruses, bacteria, fungi, parasites.
- **Chemical** – eg heavy and trace metals like lead, mercury, cadmium, arsenic, and nickel, certain electrophilic aromatic chemicals like the plasticiser bisphenol A, chemical flame retardants like brominated diphenyl ethers (BDEs), and certain halogenated pesticides like chlorpyrifos and DDT.
- **Physical** – eg heat, salt, pH shock, UV/ionising radiation.
- And also **psychological**, because psychological trauma also has physiological repercussions.

Polarity switch and shifts in metabolism

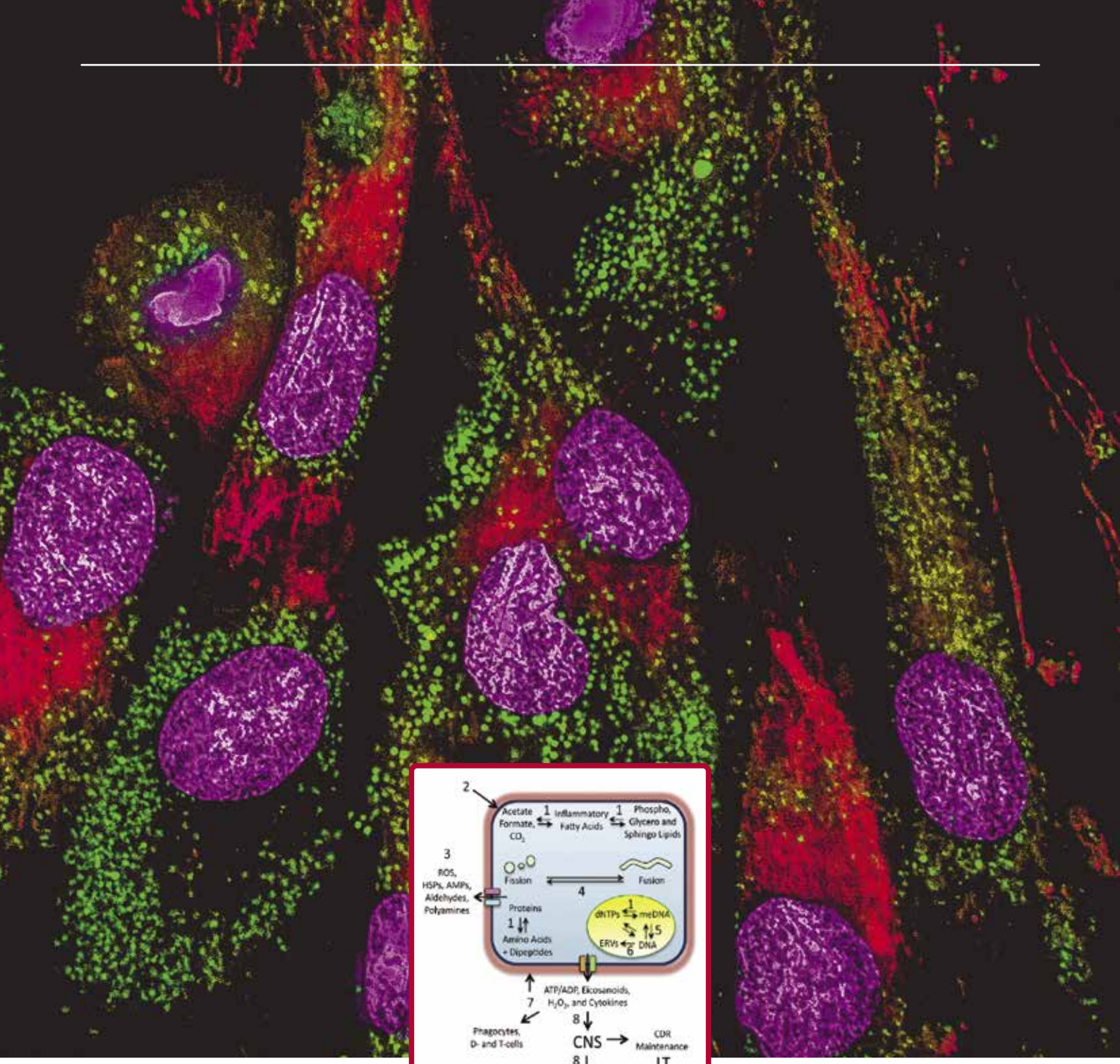
Naviaux writes that when danger is detected, mitochondria alter their cellular metabolism to shield the cell from further injury. They downregulate as a protective mechanism. The process as he describes it consists of the following steps:

1) Mitochondria decrease their



Mitochondrial research leader: Prof Robert Naviaux, MD, PhD, is a Salk-trained virologist, and molecular and cell biologist, the inventor of the popular pCL retroviral gene transfer vectors, and was trained at NIH in tumour immunology and natural killer cell biology.

His work in ecosystem dynamics has guided new work in microbiome ecology and metabolism in autism spectrum disorders. In 2011, he received a Trailblazer Award from Autism Speaks. His 2013 paper reporting preclinical studies on the role of purinergic signalling and the cell danger response in autism was ranked the #1 most-viewed report of 2013 on the Simons Foundation autism web site. He was the director of SAT1 trial, the first FDA-approved clinical trial to study the safety and test the effects of suramin, a purine-blocking drug, on behaviour and language in children with autism.



oxygen consumption to oxidise the cellular environment, inhibiting the assembly of monomeric building blocks into polymers, thus decreasing the efficiency of RNA, protein, and DNA synthesis by the infecting pathogen/insult.

2) The cell stiffens its membranes to limit the further spread of pathogens.

3) The cell releases antiviral and antimicrobial chemicals.

4) Autophagy, mitochondrial fission and mitophagy increase.

5) Changes take place in DNA methylation: S-adenosyl-methionine is directed to polyamine synthesis to assist ROS and antiviral/antimicrobial polyamine aldehyde synthesis and release, lowering the SAM/SAH ratio.

6) Endogenous retroviruses (ERVs) are mobilised.

7) ATP is released from the cell as warning to other cells that danger is afoot, becoming eATP (extracellular ATP).

8) Host behaviour alters (activity/procreation etc all take a back seat).

This leads to shifts in metabolism at various branch points. His seminal article contains two images that list many examples of these branch points. The voltage gradient across the mitochondrial membrane switches, pH shifts, intracellular conditions upregulate oxidation in the cytosol, and the cellular concentration gradient is switched 180°. A knock-on effect is that enzymatic action is altered and sometimes actually disabled, because enzymes are so pH-dependent. The repercussions of this entire process add up to what we term inflammation.

This powerful sequence of reactions is tightly choreographed to fight the threat, but the patient's own cellular response will not always be sufficient, as we know so well. Finding out the nature of the issue – whether pathogens, toxins, or otherwise – is essential to help fast-track the patient's recovery with tailored initiatives and nutrients.

Counterintuitive implications

1. Vitamin D

It is interesting to notice when one goes through the different branch points how the well-meaning advice we give may sometimes counter what the human organism knows it needs to do during this CDR process.

Naviaux explains that vitamin D metabolism, for example, is greatly altered

by the CDR. "A mitochondrial P450 enzyme, 1alpha hydroxylase, in the kidney is required to activate 25-Hydroxyvitamin D to hormonally active 1,25-Dihydroxyvitamin D". Another mitochondrial enzyme that inactivates vitamin D, 24 alpha-hydroxylase, is increased by cell danger threats in order to support inflammation. Our immediate reaction is always to raise a patient's vitamin D, but are there times when this may be counterproductive?

2. Folate and B12

Folate and B12 metabolism in the CDR also gives pause for thought, as though we are in some kind of "Alice down the rabbit hole world", where what we thought was correct is turned upon its head.

"The oxidizing conditions of the CDR increase the ratio of formyl-tetrahydrofolate to methyl-tetrahydrofolate (fTHF/mTHF) and the ratio of methylene-THF to mTHF. This favours the *de novo* synthesis of nucleotides like IMP and dTMP that require 1-carbon donation from fTHR and methylene-THF, respectively. The resulting increase in IMP synthesis can be used to make purine nucleotides like ATP for purinergic signalling. The oxidising conditions of the CDR ensure that the resulting nucleotides will be used preferentially as monomers for metabolic and signalling purposes, since assembly into polymers of RNA and DNA is chemically unfavourable" (during that phase).

Again, we so often find patients resistant to folate and B12 at times during our encounters with them: could this be to do with where they are in the CDR "journey" – their organism is telling us that MTHF/B12 is just not what they need right then?

3. Antioxidants

One last counterintuitive example of the many that Naviaux details: antioxidants. Our immediate reaction when seeing a patient in crisis is often to want to increase their oxygen levels and give them antioxidants. Could it be counterproductive to do this and neutralise their free radical reactions when the mitochondria have downregulated their respiration to allow this metabolic switch?

In a 2012 article called "Oxidative Shielding or Oxidative Stress?" (2), Dr Naviaux describes oxidative stress in the recovery process as a "response to cellular injury or attack". Antioxidant therapy "may ultimately prove harmful because it inhibits the highly evolved protective and hormetic functions of protein-catalysed oxidative shielding".

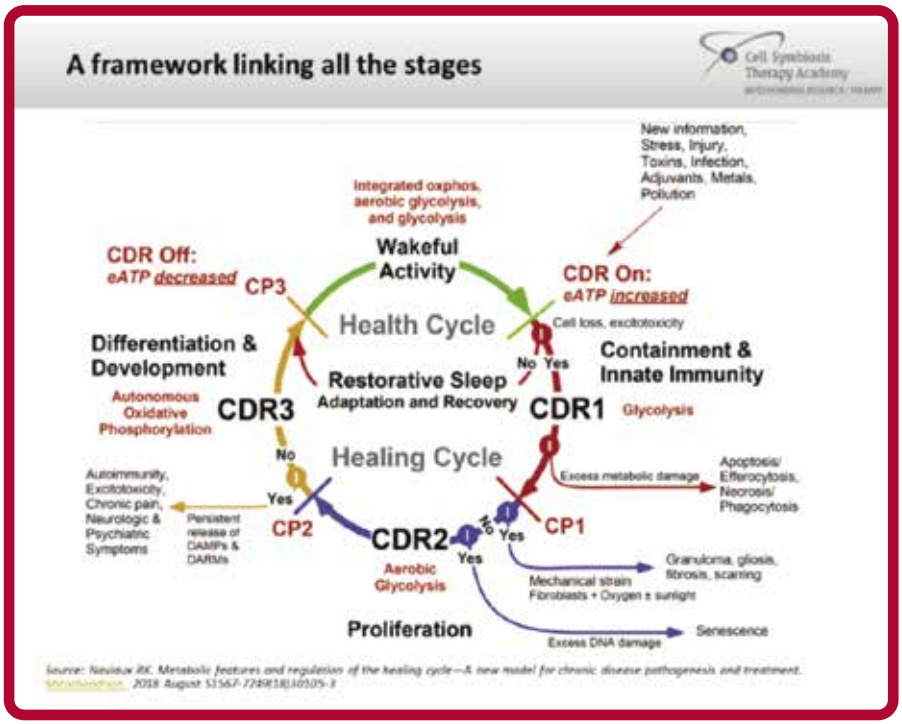
Siege metabolism: the hypometabolic response

But what happens when the CDR gets stuck, or we are unable to overcome the danger? As Naviaux describes (3): "A second step kicks in that involves a kind of siege metabolism that further diverts resources away from mitochondria and sequesters or jettisons key metabolites and cofactors to make them unavailable to an invading pathogen, or acts to sequester toxins in specialised cells and tissues to limit systemic exposure. This has the effect of further consolidating the hypometabolic state".

The three stages of the CDR

In 2018, Naviaux elaborated on the CDR. In "Metabolic features and regulation of the healing cycle – a new model for chronic disease pathogenesis and treatment" (5), he breaks down the Cell Danger Response into three stages. "We call them CDR1, CDR2 and CDR3", he explains: "These are an intrinsic part of the natural healing cycle".

The framework linking all the stages is below:



Source: Naviaux RK. Metabolic features and regulation of the healing cycle—A new model for chronic disease pathogenesis and treatment. Mitochondrion. 2018 August 5156/7-7249(18)30305-8

Naviaux posits that this is what is often termed ME or CFS.

He was in fact funded by the NIH to do a large-scale study on the CDR as it relates to ME, focusing on its metabolomics (4). He conducted the study with a large number of co-investigators, including the renowned MDs Neil Nathan, Wayne Anderson and Eric Gordon. "Metabolic features of chronic fatigue syndrome", published in 2016, traces the features of ME/CFS to the mitochondria: "We report that targeted, broad-spectrum metabolomics of plasma not only revealed a characteristic chemical signature, but also revealed an unexpected underlying biology. Metabolomics showed that chronic fatigue syndrome is a highly concerted hypometabolic response to environmental stress that traces to mitochondria and was similar to the classically studied developmental state of dauer [means "persistence" in German]... This...may ultimately represent a fundamental response to oppose the spread of persistent viral and intracellular bacterial infections" (4). The appendix of that metabolomics study provides fascinating detail, especially on differences in the results for males and females.

He clearly differentiates cell energetics, metabolites, and autonomy by phase of the CDR. It is important to remember that the cells/mitochondria will not all be in the same phase in each organ; there is likely to be a mix across the body, depending on the patient's predisposing conditions:

- **CDR1** is distinguished by glycolysis. The function of CDR1 is the activation of innate immunity, intruder and toxin detection and removal, damage control, and containment. The result is a dramatic reduction in cell death when preconditioned cells in CDR1 are exposed to potentially lethal insults.
- **CDR2** is characterised by upregulated aerobic glycolysis. The prime function of CDR2 is biomass replacement.

Every organ and tissue has an optimum number and distribution of differentiated cell types that are needed for healthy organ function. When cells are lost, they must be replaced, or organ function cannot be fully restored. Once the damage associated with the initial injury, infection, or toxin exposure has been cleared or contained in CDR1, the cells that were lost need to be replaced. The mitochondria in this phase still process

Healing Cycle Research

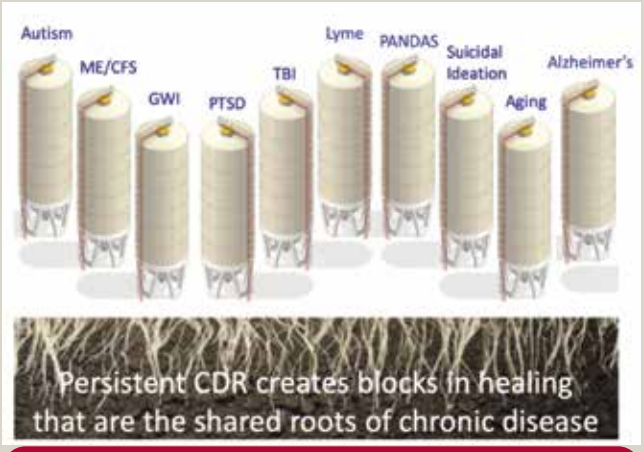
"Research in our lab has led to a new understanding of the ancient biology that underlies the circle of injury and recovery. New medicines and treatments are being developed that can remove the blocks to healing and help people get back on the road to recovery from disorders that were once thought to be permanent and irreversible", says the Naviaux Lab.

Prof Naviaux and colleagues are focused on writing what they call "the Second Book of Medicine", dealing with the treatment and prevention of chronic illness – something that, up to now, conventional medicine has failed to effectively address.

"When blocks to healing occur, chronic illness results. Now 40% of children and 60% of adults must live with a chronic illness", they say (http://naviauxlab.ucsd.edu/the-28th-amendment-project).

"Research in the Naviaux Lab has led us to the conclusion that a simple removal of a trigger, or treatment of a target that appears to be the 'cause' of a symptom in a chronic disease, almost never leads to a cure. Instead, the symptom is palliated, but at the cost of having to take a medicine for life in order to keep that symptom in check. For example, insulin does not cure diabetes, and statins do not cure high cholesterol. These 'pathogenesis-based' treatments almost never allow a person to shed their chronic disease and return to a drug-free state of health. Why?"

Instead, Naviaux are exploring the use of "salugens" that will, as integrative interventions do, support the Healing Cycle. " Salugens are interventions that promote the completion of the healing cycle, restore health, decrease mortality, and create heightened states of health and resilience. Salugens create an integrated, multisystem resistance to future chronic illness. Salugens need not be restricted to drugs. Exercise is a salugen. Adaptogens are salugens. Certain electrophysiologic interventions designed to promote healing associated with slow wave sleep are salugens".



Silos of Knowledge: study of a single disease can show how it is different from all other diseases. However, it is knowledge of how complex disorders are the same that will lead to new cures of disorders that were previously thought to be permanent and irreversible. CDR – cell danger response, ME/CFS -myalgic encephalomyelitis/ chronic fatigue syndrome, GWI – Gulf War Illness, PTSD – post-traumatic stress disorder, TBI – traumatic brain injury, PANDAS – paediatric acute neurologic disorder associated with streptococcal infection.

• **Read more and follow the Naviaux Lab's research at https://naviauxlab.ucsd.edu.**

oxygen and electrons, but instead of using the potential energy gradient for synthesising ATP by oxidative phosphorylation, "they dissipate the energy gradient by releasing metabolic intermediates needed for polymer synthesis and cell growth".

Fascinating – as the exact function of the "oxidative ferment" identified by Dr Otto Warburg (also termed "The Warburg Effect") as a key factor in cancer as far back as the 1920s (for which he won the Nobel Prize in 1931) had always been somewhat opaque (6). This does of course explain proliferation – if it continues unchecked, and Naviaux terms this stage "Proliferative disorders".

■ **CDR3** – autonomous oxidative phosphorylation. Cells that enter CDR3 stop dividing and begin establishing cell-cell connections with their neighbours. Their mitochondria repolarise, Naviaux hypothesises, taking on the anti-inflammatory phenotype needed for differentiated cell function and oxidative phosphorylation.

An entirely new perspective on mitochondrial pleomorphism

Describing mitochondrial pleomorphism to this degree is entirely new. Naviaux has classified disorders along the three CDR phases, terming them "Innate immune disorders", "Proliferative disorders", and "Differentiation disorders" (for the classification, please see Table 1 in his 2018 article). Investigating how applicable this CDR matrix is for each of these disorders will require far more research, but it certainly does help to explain many of the conundrums we have long been faced with as practitioners, and provides pointers to a way forward depending on which stage the patient appears to be in.

This second article also reminds us how many different stress response systems the mitochondria are responsible for: apoptosis, lipid raft formation, the unfolded protein response, transglutaminase activation, liver xenobiotic detoxification, sensory processing, ANS dynamics – the list is astonishing. Our mitochondria really are the orchestrators of our cells. And when they have to downregulate for "the greater good", in protective responses, it is no surprise that so many systems go awry. The question is what has triggered the response in the first place, and to address that, rather than just the symptoms.

It will also be important to detect when they have got "stuck on automatic", and how this alters the therapeutic response.

There is much work ahead in this embryonic field, but further studies have been approved, with the involvement now also of the heavyweight Prof Ron Davis, Director of Stanford's Genome Technology Centre. His own son has been locked in the most severe form of ME for many years, and he freely admits that this gives him perhaps the greatest motivation of all to decipher the language of cellular shut-down, and reverse it.

Relevance going forward in "the world after COVID-19"

We do all need to follow this research, especially with the ravages the SARS-CoV-2 virus is likely to leave in its wake. Extrapolating from a 2011 study entitled "Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study", *The Canary* has calculated that between 408,000 and 3,570,000 people in the US alone could experience severe ME-like symptoms a year after getting infected by SARS-CoV-2 (7).

To what extent may this be due to a CDR that has become "stuck", as Naviaux hypothesised back in 2011, calling it "anachroadaptive mitocellular dysfunction"? Anti-purinergic therapy has shown great promise in unblocking the CDR in a further study Naviaux has run, but we all need to put our heads together on this going forward, as we are possibly moving into an entirely new field of pathology. Research into CDR may hold many of the answers. IHCAN

About the author

GILIAN CROWTHER, MA (Oxon), FBANT, mNNA, is a naturopath and registered nutritional therapist with a clinic in London. She studied and gained qualifications in complementary therapy in Germany for many years before taking up further training in the UK. As Director of Research for the Academy of Nutritional Medicine (www.aonm.org), Gilian is responsible for clinical training on the range of tests they offer. She regularly holds talks on nutrition, mitochondrial therapy, and testing.