

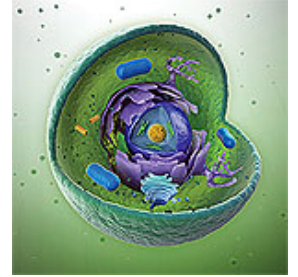
Life Extension Magazine February 2011

# REPORT

## Generate Fresh Mitochondria with PQQ

By Perry Marcone

In 1983, **Life Extension®** introduced a relatively little-known compound called **coenzyme Q10**. Our review of the literature back then had unearthed data confirming its power to boost the health and energy output of the **mitochondria**.



Today, scientists recognize **mitochondrial dysfunction** as a key biomarker of aging.<sup>1-6</sup> To take one instance, researchers have recorded evidence of **50% more** mitochondrial damage in the brain cells of humans over 70 compared to middle-aged individuals.<sup>7</sup> Mitochondrial dysfunction and death are now definitively linked to the development of virtually all killer diseases of aging, from **Alzheimer's** and **type 2 diabetes** to **heart failure**.<sup>8-11</sup>

The good news is that mitochondrial dysfunction can be *reversed*.<sup>12</sup> The scientific literature is now filled with studies documenting the therapeutic power of **CoQ10** to thwart degenerative disease by boosting mitochondrial health and bioenergetic (energy-producing) capacity.<sup>13-16</sup>

The latest advance in the area of **mitochondrial bioenergetics** is the coenzyme **pyrroloquinoline quinone** or **PQQ**.

PQQ's critical role across a range of biological functions has only gradually emerged. Like CoQ10, it is a micronutrient whose antioxidant capacity provides extraordinary defense against mitochondrial decay.

But the most exciting revelation on PQQ emerged early in 2010, when researchers found it not only protected mitochondria from oxidative damage—it stimulated growth of fresh **mitochondria!**<sup>17</sup>

In this article, you will learn of this novel coenzyme's ability to combat mitochondrial dysfunction. You will find out how it protects the brain, heart, and muscles against degenerative disease. You will also discover its potential to **reverse** cellular aging by activating **genes** that induce mitochondrial biogenesis—**the spontaneous formation of new mitochondria in aging cells!**

## PQQ: A Breakthrough in Cellular Anti-Aging



PQQ is ubiquitous in the natural world. Its presence in *interstellar stardust* has led some experts to hypothesize a pivotal role for PQQ in the evolution of life on Earth.<sup>18</sup>

It has been found in all plant species tested to date. Neither humans nor the bacteria that colonize the human digestive tract have demonstrated the ability to synthesize it.<sup>19</sup> This has led researchers to classify PQQ as an **essential micronutrient**.<sup>20</sup>

PQQ's potential to stimulate **mitochondrial biogenesis** was foreshadowed by repeated early findings indicating its central role in growth and development across multiple forms of life.

It has been shown to be a potent growth factor in plants, bacteria, and higher organisms.<sup>21,22</sup> Pre-clinical studies reveal that when deprived of dietary PQQ, animals exhibit stunted growth, compromised immunity, impaired reproductive capability, and most importantly, **fewer mitochondria in their tissue**. Rates of conception, the number of offspring, and survival rates in juvenile animals are also significantly reduced in the absence of PQQ.<sup>23-25</sup> Introducing PQQ back into the diet reverses these effects, restoring systemic function while simultaneously increasing mitochondrial number and energetic efficiency.

## Optimal Mitochondrial Defense

As the primary engines of almost all bioenergy production, the mitochondria rank among the physiological structures *most* vulnerable to destruction from *oxidative* damage. PQQ's formidable free radical-scavenging capacity furnishes the mitochondria with superior antioxidant protection.

At the core of this capacity is an extraordinary molecular stability.<sup>30</sup> As a bioactive coenzyme, PQQ actively participates in the energy transfer within the mitochondria that supplies the body with most of its bioenergy (like **CoQ10**).

*Unlike* other antioxidant compounds, PQQ's exceptional stability allows it to carry out thousands of these electron transfers without undergoing molecular breakdown. It has been proven especially effective in neutralizing the ubiquitous **superoxide** and **hydroxyl** radicals.<sup>31</sup> According to the most recent research, "PQQ is **30 to 5,000 times** more efficient in sustaining redox cycling (mitochondrial energy production) . . . than other common [antioxidant compounds], e.g. ascorbic acid."<sup>21</sup> A consistent finding in the scientific literature is that nutrients like PQQ provide more wide-ranging benefits than conventional antioxidants the general public relies on.

## Anti-Aging Armor for the Most Energy-Intensive Organs

PQQ's dual capacity as a cell *signaling modulator* and a superior antioxidant renders it optimally effective in combating degenerative disease and age-related declines in the body's most energetic organs: the **heart** and **brain**.

The revelation of its ability to favorably affect system-wide cell development, metabolism, and mitochondrial biogenesis affords an explanation for a wealth of data on its neuroprotective and cardioprotective benefits.

## Neuroprotection

PQQ has been shown to optimize health and function of the entire central nervous system. It reverses cognitive impairment caused by chronic oxidative stress in pre-clinical models, improving performance on memory tests.<sup>32</sup> It has also been shown to safeguard the "Parkinson's disease gene," DJ-1, from *self-oxidation* —an early step in the onset of disease.<sup>33</sup>

Reactive *nitrogen* species (RNS), like reactive oxygen species, impose severe stresses on damaged neurons.<sup>34</sup> They arise spontaneously following stroke and spinal cord injuries and have been shown to account for a substantial proportion of subsequent long-term neurological damage. PQQ *suppresses* RNS in

experimentally induced strokes.<sup>35</sup> It also provides additional protection by blocking gene expression of inducible nitric oxide synthase (iNOS), a major source of RNS, following spinal cord injury.<sup>36</sup>

PQQ powerfully protects brain cells against oxidative damage following **ischemia-reperfusion injury**—the inflammation and oxidative damage that result from the sudden return of blood and nutrients to tissues deprived of them by stroke.<sup>37</sup> Given immediately before induction of stroke in animal models, PQQ significantly reduces the size of the damaged brain area.<sup>38</sup>

PQQ also interacts in a beneficial manner with our brain's neurotransmitter systems. In particular, PQQ protects neurons by modifying the important NMDA receptor site.<sup>39,40</sup> NMDA is a powerful mediator of "excitotoxicity," a response to long-term overstimulation of neurons that is associated with many neurodegenerative diseases and seizures.<sup>41-43</sup> PQQ also protects against neurotoxicity induced by other toxins, including **mercury**.<sup>44,45</sup>

#### WHAT YOU NEED TO KNOW: PQQ

- **Mitochondrial dysfunction** has been definitively linked to virtually all killer diseases of aging, from **Alzheimer's disease** and **type 2 diabetes** to **heart failure**.
- Researchers have recorded evidence of greater mitochondrial damage in the brain cells of humans over 70 compared to those in their early 40s.
- Many scientists believe *mitochondrial* longevity determines *overall* longevity.
- A next-generation **coenzyme** is being introduced called *pyrroloquinoline quinone* or **PQQ** that has been shown to induce **mitochondrial biogenesis**—the growth of new mitochondria in aging cells.
- While **CoQ10** *optimizes* mitochondrial function, PQQ activates genes that govern mitochondrial reproduction, protection, and repair.
- PQQ also affords potent cardioprotection and defense against neuronal (brain) degeneration.
- Published studies show that **20 mg** of PQQ plus **300 mg** of CoQ10 may *reverse* age-related cognitive decline in aging humans.



A mounting body of evidence points to PQQ as a potent intervention in **Alzheimer's disease** and **Parkinson's disease**. Both are triggered by accumulation of abnormal proteins that initiate a cascade of oxidative events resulting in brain cell death. PQQ prevents development of a protein (alpha-synuclein) associated with Parkinson's disease.<sup>46</sup> It also protects nerve cells from the oxidizing ravages of the amyloid-beta protein linked with Alzheimer's disease.<sup>47</sup> A 2010 study revealed that PQQ could prevent formation of amyloid beta molecular structures.<sup>48</sup>

PQQ has also been shown to protect memory and cognition in both aging animals and humans.<sup>49,50</sup> It stimulates production and release of nerve growth factor in cells that support neurons in the brain.<sup>51</sup> This may partially explain why PQQ supplementation of aging rats resulted in marked improvement of their memory function.<sup>49</sup>

In humans, supplementation with **20 mg per day** of PQQ resulted in improvements on tests of higher cognitive function in a group of middle-aged and elderly people.<sup>50</sup> These effects were significantly amplified when the subjects also took **300 mg** per day of **CoQ10**.

# REPORT

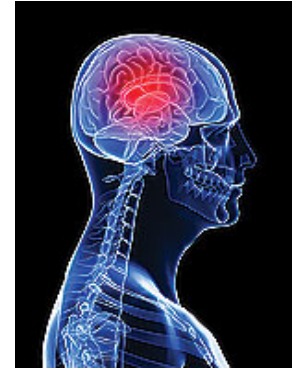
## Generate Fresh Mitochondria with PQQ

By Perry Marcone

### MITOCHONDRIAL FUNCTION AND LONGEVITY: THE DEFINITIVE LINK

In cell biology, mitochondria are unique among other cellular components in one vital aspect: they possess their own *primitive* DNA, distinct from the DNA housed within the cell nucleus that you normally think of as the building block of all living organisms.

Mitochondrial DNA closely resembles bacterial DNA, the result of an evolutionary legacy.<sup>55</sup> Biologists believe that at one time our mitochondria existed as separate, highly energetic organisms. Our primordial ancestor cells aggressively engulfed and *incorporated* these “proto-mitochondria” into their own internal structure. This furnished our cellular progenitors with two powerful evolutionary advantages: it harnessed the ability of proto-mitochondria to produce vast quantities of energy from oxygen—and served to boost cellular **longevity**.



This simple fact has profound implications for the science of anti-aging.

Why? You already know that cells in your body have the capacity to divide and replicate themselves owing to the presence of nuclear DNA. If mitochondria possess their own DNA, it follows that they should also have the ability to replicate themselves and increase their number within a single human cell.

This turns out to be the case: human cells may house anywhere from **2** to **2,500** mitochondria,<sup>56-58</sup> depending on tissue type, nutrition, antioxidant status, and other factors. Put differently, one cell may contain over *1,000 times more mitochondria* than another.

The more high-functioning mitochondria in your body, the greater your overall health and longevity. This is no longer a matter of conjecture. A growing number of cell biologists now espouse the theory that mitochondrial number and function *determine human longevity*.<sup>59-61</sup>

The problem is that the scientifically validated methods available to spontaneously increase the number of new mitochondria in our aging bodies are exceedingly difficult. To date, the only known ways to reliably stimulate mitochondrial biogenesis—sustained **calorie restriction** or **strenuous physical activity**—are far too rigorous and impractical for most aging individuals.

A nutrient with the power to safely trigger mitochondrial biogenesis would naturally mark an extraordinary advance in the quest to halt and reverse cellular aging.

**PQQ** has emerged as that nutrient.

## Cardioprotection

As with stroke, damage in heart attack is inflicted via ischemia-reperfusion injury. Supplementation with PQQ reduces the size of damaged areas in animal models of acute heart attack (myocardial infarction).<sup>52</sup> This occurs whether the supplement is given before or after the ischemic event itself.

To further investigate this potential, researchers at the VA Medical Center at UC-San Francisco compared PQQ with **metoprolol**, a beta blocker that is standard post-MI clinical treatment. Given alone, both treatments reduced the damaged areas' size and protected against heart muscle dysfunction. When they were given together, the left ventricle's pumping pressure was enhanced. The combination also increased mitochondrial energy-producing functions—but the effect was small compared with PQQ alone! And only PQQ favorably reduced lipid peroxidation. The remarkable conclusion: "PQQ is superior to metoprolol in protecting mitochondria from ischemia/reperfusion oxidative damage."<sup>53</sup>

Subsequent research from the same team has demonstrated that PQQ helps heart muscle cells resist acute oxidative stress.<sup>54</sup> The mechanism? Preserving and enhancing *mitochondrial function*.

#### WHY YOUR MITOCHONDRIA ARE HIGHLY EXPOSED TO LETHAL MUTATION

Cell aging occurs as each cell's ability to reproduce itself inexorably declines. This decline is in turn associated with the gradual degradation and destruction of the DNA complex.

Overlooked in this process is the equally important role of the mitochondria's robust ability to reproduce as you age.

Just as degradation of the cellular DNA complex ultimately leads to senescence and death, degradation of the mitochondrial DNA complex leads to the death of the mitochondria and the ultimate extinction of the cell—and the "host" organism.

This death spiral of genetic degradation is accelerated in the mitochondria by the very physiological function they must perform. As the nuclear generators responsible for almost all bioenergetic production, mitochondria are the site of enormous oxidative activity. A nearly incalculable number of electrons are constantly flowing within the mitochondria, throwing off an equally enormous number of free radicals. This makes them highly vulnerable to biochemical insults.

There is an additional threat, as scientists have discovered over the past several decades: relative to nuclear DNA, ***mitochondrial DNA possesses few defenses against free radical damage.***<sup>62,63</sup>

Cellular DNA is protected by numerous "guardian" proteins (histones and repair enzymes) that act to blunt the impact of free radicals. No such repair systems exist to protect mitochondrial DNA.<sup>62,63</sup>

Cellular DNA also enjoys superior structural defenses. It is housed within a protective double-membrane that separates it from the rest of the cell. This double-membrane is complemented by a dense matrix of filament proteins called the nuclear lamina, a kind of hard shell casing to further buffer DNA from external impacts.

By comparison, mitochondrial DNA is left almost entirely exposed: it attaches directly to the inner membrane where the mitochondria's electrochemical furnace rages continuously, generating an enormous volume of toxic reactive oxygen species.



Accordingly, mitochondrial DNA mutates at a much higher rate than cellular DNA.<sup>64</sup> When you consider that the mitochondria supply at least **95%** of the energy required for all physiological processes in your body, the need to maintain the integrity of mitochondrial DNA takes on even greater urgency. All aging humans should take every step to safeguard the genes that regulate healthy mitochondrial proliferation from lethal mutation. This is supported by an abundance of scientific studies linking genetic *mutation* within the mitochondria to human aging.<sup>65-67</sup>

PQQ's extraordinary antioxidant capacity represents a powerful new intervention that may effectively reinforce the mitochondria's limited defenses.

## Summary

**Mitochondrial dysfunction** has been definitively linked to virtually all killer diseases of aging, from **Alzheimer's disease** and **type 2 diabetes** to **heart failure**.

Researchers have recorded evidence of greater mitochondrial damage in the brain cells of humans over 70 compared to those in their early 40s. The health and function of these cellular energy generators is now considered so vital that many scientists believe *mitochondrial* longevity determines *overall* longevity in aging humans.

In a revolutionary advance, an essential coenzyme called *pyrroloquinoline quinone* or **PQQ** has been shown to induce **mitochondrial biogenesis**—the growth of new mitochondria in aging cells!

While **CoQ10** *optimizes* mitochondrial function, PQQ activates genes that govern mitochondrial reproduction, protection, and repair. PQQ also affords potent cardioprotection and optimal defense against neuronal degeneration. Published studies show that **20 mg** of PQQ plus **300 mg** of CoQ10 may *reverse* age-related cognitive decline in aging humans.

### PQQ ACTIVATES SIGNALING MOLECULES

A team of researchers at the University of California decided to analyze PQQ's influence over cell signaling pathways involved in the generation of new mitochondria.<sup>17</sup>

Their work, published in 2010, led to several extraordinary discoveries.

They found that PQQ's critical role in growth and development stems from its unique ability to activate **cell signaling pathways** directly involved in cellular energy metabolism, development, and function. Cells undergo **spontaneous mitochondrial** biogenesis through the effects of **three signaling molecules** activated by PQQ:

PQQ activates expression of **PCG-1 $\alpha$**  (peroxisome proliferator-activated receptor gamma coactivator 1-alpha). PCG-1 $\alpha$  is a "master regulator" that mobilizes your cells' response to various external triggers. It directly stimulates genes that enhance mitochondrial and cellular respiration, growth, and reproduction. Its capacity to upregulate cellular metabolism at the genetic level favorably affects **blood pressure**, **cholesterol** and **triglyceride** breakdown, and the onset of **obesity**.<sup>26</sup>





PQQ triggers a signaling protein known as **CREB** (cAMP-response element-binding protein). CREB plays a pivotal role in embryonic development and growth. It also beneficially interacts with histones, molecular compounds shown to protect and repair cellular DNA.<sup>27</sup> CREB *also* stimulates the growth of new mitochondria.

PQQ regulates a recently discovered cell signaling protein called **DJ-1**. As with PGC-1 $\alpha$  and CREB, DJ-1 is intrinsically involved in cell function and survival. It has been shown to **prevent cell death** by combating intensive antioxidant stress<sup>28,29</sup> and is of particular importance to brain health and function. DJ-1 damage and mutation have been conclusively linked to the onset of **Parkinson's disease** and other neurological disorders.

These findings shed light on the results of prior studies where a PQQ deficiency in juvenile mice, for example, resulted in elevated plasma glucose concentrations, a **20-30%** reduction in the number of mitochondria in the liver, and consequent impairment in oxygen metabolism.<sup>23</sup> These are hallmark indicators of mitochondrial dysfunction. Additional animal models also suggested significant alterations in mitochondrial numbers.<sup>25</sup> Taken together, these results confirm PQQ's power to significantly boost mitochondrial number and function—the key to cellular anti-aging and longevity.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

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