

REPORT

Conclusion of a 3-Part Series on Cellular Bioenergetics and CoQ10
How CoQ10 Protects Brain Cells

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The source of life and death for neurons (nerve cells) lies in the mitochondria. These tiny organelles generate the neuron's energy and control its death. The mitochondria tend to develop defects with age. As these defects accumulate, they cause increasing mitochondrial dysfunction in the nondividing cells of the brain, heart and muscle. The result is reduced cellular energy production and increased cell death, as occurs in neurodegenerative disease and stroke. Recent research provides us with an opportunity to protect against this destructive process by minimizing mitochondrial dysfunction and preventing other pathological events that cause brain cells to die.

Life Extension magazine published the first two installments of this three part series in the April, 2000 and February, 2001 issues. The articles were titled "How CoQ10 Protects Your Cardiovascular System" and "Cellular Nutrition for Vitality and Longevity" (April 2000), "Bioenergetic Therapy for Aging" and "The Metabolic Syndrome" (February 2001). These features detail CoQ10's role in cellular bioenergetics, and provide a foundation for this final installment.

A review article in Brain Research Reviews on the role of the mitochondria in neurodegeneration notes that "it is becoming clear that subtle functional alterations in these essential cellular dynamos can lead to insidious pathological changes in neurons" (Cassarino DS et al., 1999). The authors outline a theory of neurodegeneration based upon a vicious cycle of mitochondrial DNA mutation, bioenergetic decline and oxidative stress. Their recommendations echo the antiaging functions of CoQ10 discussed in the previous installments of this series, namely improving cellular respiration, normalizing or preventing oxidative stress, and inhibiting programmed cell death.

If aging and neurodegeneration have similar basic causes, neurodegeneration research could turn out to be a laboratory for understanding the processes of aging and how to influence them. However, the physiology of the brain is in certain ways unique, and its pathologies present some unique mechanisms and features.

The brain is especially vulnerable to oxidative stress due to its rich oxygen supply and high fatty acid content. It would seem logical that the brain's antioxidant defense system would be especially robust. Unfortunately, the opposite is the case. The brain is relatively underdefended against oxidative stress. Consequently neurons, which are for the most part irreplaceable, gradually accumulate oxidative damage over time.

The brain's vulnerability increases with age. Most of the fatty acid content of the brain is contained in the membranes that surround brain cells, their extensions (such as axons) and the mitochondria. As we age, more of these lipids become polyunsaturated, which makes them more susceptible to lipid peroxidation. Polyunsaturated fats exposed to the brain's rich supply of oxygen and oxygen byproducts are like dry tinder near fire.

Oxidative stress and bioenergetic failure are fundamental to neurodegeneration. Scientists use neurotoxins that work in just these ways to mimic neurological diseases in lab animals. CoQ10 protects lab animals from the effects of such neurotoxins, according to a series of studies by neurologist M. Flint Beal and colleagues at the Massachusetts General Hospital and Harvard Medical School. They found that the neurotoxins malonate, 3-NP and MTPT inflicted significantly less brain damage on animals treated with CoQ10. Beal's studies provided the first demonstration that oral CoQ10 supplements exert neuroprotective effects in the living brain, and significantly raise CoQ10 levels in brain tissue and brain mitochondria.

Excitotoxicity

These neurotoxins also lead to a major cause of cell death in neurodegenerative disease called excitotoxicity. The neurotransmitter

glutamate normally transmits excitatory impulses. In neurodegeneration the brain becomes chronically oversensitive to glutamate, which then acts as a slow-acting “excitatory toxin” on brain cells.

A seminal paper by NIH (National Institutes of Health) scientists in 1988 proposed that excitotoxicity develops when the energy level of neurons declines, and subsequent research has borne out their theory. Studies show that CoQ10 protects against excitotoxicity by raising neuronal energy levels. Italian scientists discovered that CoQ10 protects neurons cultured in glutamate from excitotoxicity. Beal’s group extended these findings to rats. They gave the rats a neurotoxin (malonate) that induces excitotoxic brain lesions. When the rats were fed CoQ10 in their chow for 10 days before exposure to the toxin, lesions were reduced by 30%. CoQ10 also restored energy production in the neurons to nearly normal levels.

Newly published research suggests that CoQ10 can protect brain cells from neurotoxicity and excitotoxicity, while even powerful antioxidants cannot. CoQ10 proved highly effective, while simple antioxidants were ineffective, in protecting PC-12 cells (neuron-like rat adrenal cells commonly used in neurobiological research) from the excitotoxic effects of glutamate and from the Parkinson’s disease-like effects of the neurotoxin MPP+. L-deprenyl (the drug selegiline) also proved effective, though not as effective as CoQ10. The scientists conclude that there may be “a greater role for mitochondrial dysfunction and cellular energy than free radicals, in both models of cell death. And, it seems that energy compromise plays a large role in the progression of Parkinson’s disease” (Mazzio E et al., 2001).

Parkinson’s disease

In Parkinson’s disease, cell death is highly selective. Neurons that produce the neurotransmitter dopamine die in a part of the brain that coordinates movement. This depletes dopamine stores and leads to muscle rigidity, tremor and difficulty initiating movement.

The specific brain region affected in Parkinson’s disease, the substantia nigra, has the highest level of mitochondrial DNA mutation in the brain. Evidence is mounting that mitochondrial DNA mutations cause cellular respiration to malfunction in Parkinson’s disease, exactly as Linnane’s theory would predict (see sidebar “A Model of Bioenergetic Aging”). Parkinson’s disease patients show defective cellular respiration in the first complex of the cellular respiratory chain.

Beal and colleagues found that the bioenergetic deficit in Parkinson’s disease patients correlates strongly with CoQ10 levels. In follow-up research, they tested CoQ10 on mice treated with a neurotoxin (MPTP) whose effects mimic Parkinson’s disease. The toxin caused significantly less damage to the dopamine system in the brains of mice that had been fed CoQ10 for the previous five weeks.

Beal’s group also tested the bioenergetic effect of oral CoQ10 supplements in Parkinson’s disease patients. They found that CoQ10 restored the depressed activity of the first complex of the cellular respiratory chain to approximately normal levels, and was most effective at 600 mg per day. The scientists emphasized, however, that a larger study is required to determine whether the trend toward significance of these results will be validated. Furthermore, a new study shows that oral CoQ10 also increases the activity of the second complex of the cellular respiratory chain in the brains of normal mice.

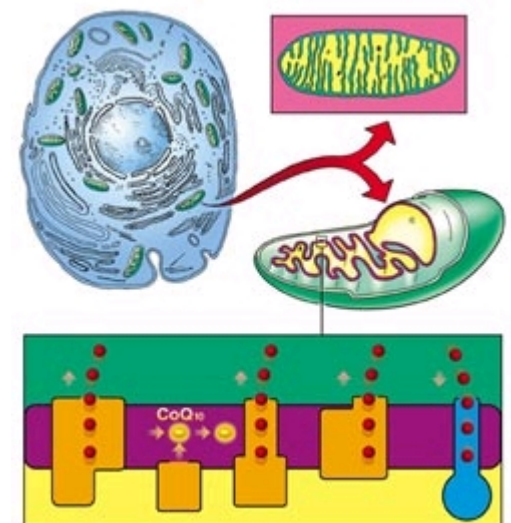
Scientists hypothesize that the bioenergetic defect in Parkinson’s disease “lowers the threshold” for programmed cell death. Energetically deficient neurons are less able to tolerate oxidative stress, which then triggers the cellular “decision to die.” Oxidative stress is particularly high even under normal conditions in the region of the brain affected by Parkinson’s disease, which may help explain why additional oxidative stress depresses cells in that particular region beyond the threshold for programmed cell death.

Huntington’s disease

Huntington’s is an inherited genetic disease that destroys neurons in brain regions governing movement. Symptoms include involuntary movements, lack of coordination and cognitive difficulties.

Huntington’s disease is thought to involve a bioenergetic defect. A pilot study conducted by Beal and associates showed that energy production in the central nervous system and muscle of Huntington’s disease patients is impaired. After two

Cellular Energy Generation



Structure of a cell (upper left), with detail of a mitochondrion (upper right). The cellular respiratory chain (bottom) generates energy.

Mitochondria are the power plants of the cell. They transform oxygen and nutrients into energy and water through a process called cellular respiration. The many finger-like folds in the mitochondrial inner membrane house respiratory chains (bottom panel) where energy is produced. CoQ10 (yellow) carries electrons across the chain while pumping protons (red) through the inner membrane (purple). The return flow of protons into the last component of the chain (blue) drives synthesis of ATP, the energy storage molecule.

or more months of CoQ10 supplementation (360 mg per day), 83% of patients showed significant improvements in biochemical markers of energy production.

In 1997, a multicenter clinical trial began comparing CoQ10 and the drug remacemide, each at 600 mg per day, in early stage Huntington's disease. The results of this two and a half year study are due to be released in mid August as this magazine goes to press. Preliminary media reports indicate that the drug remacemide (a glutamate blocker) had no effect on the decline in Total Functional Capacity of Huntington's Disease patients, and was found to confer no clinical benefit. On the other hand, CoQ10 slowed the decline by 13%, and also slowed decline on the Huntington's Disease Independence Scale by 17%. Reports indicate that these results showed a trend toward significance but are regarded as inconclusive. The Huntington Study Group, which organized the study, hopes to conduct a larger trial in order to determine whether CoQ10 therapy does significantly reduce the rate of decline in the early stages of the disease.

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Alzheimer's disease

Alzheimer's disease is the most common adult-onset dementia. In recent years researchers have discovered many of the mechanisms involved in the disease, but we cannot yet clearly separate causes from effects in this complex pathology. The theories we discuss are necessarily quite speculative.



The main effects of Alzheimer's disease on brain tissue are extensive neuron loss and insoluble fibrous deposits called senile plaques and neurofibrillary tangles. The core of the plaques is a toxic protein, amyloid-beta, that assails cells on several fronts. Amyloid-beta generates oxidative stress, damages mitochondrial DNA, impairs cellular bioenergetics, and alters proteins so as to form neurofibrillary tangles.

A number of recent studies have found that the degree of disability in Alzheimer's disease patients correlates with impairment of energy metabolism in the brain. In fact, a new study suggests that cellular energy production may be a better indicator than senile plaques of Alzheimer's disease severity. This study of Alzheimer's patients in a nursing home found that their degree of clinical disability correlated with a mitochondrial abnormality involved in cellular respiration, but did not correlate with the density of senile plaques.

Together with amyloid-beta, a potent free radical called peroxynitrite oxidizes lipids in neuronal membranes. This generates the highly toxic byproduct HNE that is found in excess in multiple regions of the Alzheimer's disease brain. HNE kills brain cells directly, and also indirectly by making them more vulnerable to excitotoxicity. As we have seen, the co-antioxidants coQ10 and vitamin E protect cell membranes from lipid peroxidation, and coQ10 has been found to reduce peroxynitrite damage and HNE formation in the bloodstream.

We do not know whether Alzheimer's disease arises from a single underlying cause. An interesting multiple-factor theory was published in the journal *Gerontology* (Ying W, 1997). According to this theory, Alzheimer's disease develops from four causes: imbalances in APP (amyloid precursor protein) and calcium, oxidative damage and bioenergetic deficit. The author cites studies showing that each of the factors reinforces and is reinforced by each of the other factors. This "deleterious network," as the author calls it, potentially fits the therapeutic profile of coQ10. However, coQ10 has never been included in a clinical trial for Alzheimer's disease. The reasons for this may not be scientific ones, as discussed at the end of this article.

While we do not yet know whether coQ10 has a place in Alzheimer's disease prevention or therapy, a synthetic analogue of the coQ10 family called idebedone has yielded impressive results in several European and Japanese clinical trials for Alzheimer's disease and other dementias. According to the authors of a German study of the drug, idebedone "acts on the brain by increasing the cerebral energy supply and by protecting the cell membranes against lipid peroxidation" (Weyer G et al., 1997). This study tested two dosages of idebedone on patients suffering from mild to moderate Alzheimer's disease. A total of 247 patients completed the well-designed six month long clinical trial.

Patients were evaluated on the international Alzheimer's Disease Assessment Scale (ADAS). On average, patients taking the higher dose of idebedone improved by 2.3 points on the 120 point scale as a result of treatment. The more severe the disease was at the beginning of the study, the more the patient improved, on average. Those patients who began the study with an ADAS score of at least 20 points showed gains averaging 4.1 points compared to placebo. The largest gains were on cognitive tasks, reaching 6.9 points compared to placebo on the 50 point ADAS Cognitive Scale in patients with the most severe disease (total ADAS score of at least 50 points) taking the higher dose. Of course the results of this study are not transferable to coQ10. The drug idebedone is not available in the U.S.

In the next section we turn our attention from chronic neurodegenerative diseases to the sudden attacks, loosely called strokes, seen in cerebrovascular disease.

The Ischemic Cascade

The reduction in blood flow (ischemia) during a stroke triggers a sequence of events called the "ischemic cascade." This cascade is reversible up to a point but ultimately leads to cell death. While the cascade is not fully understood and may unfold differently under different circumstances, the following events are commonly observed.

Stroke

The circulation of blood through the brain delivers a constant supply of oxygen, glucose and nutrients to brain cells. When the steady flow of blood through a portion of brain tissue ceases—as from a clot or hemorrhage—metabolism rapidly fails in brain cells. After a few minutes without blood, neurons suffer irreversible injury (see sidebar “The Ischemic Cascade”).

However, a stroke does not cut off blood supply uniformly. Rather, circulation falls off toward the core of the affected area, where little or no blood may flow. Cells in the core tend to die quickly through necrosis. These cells break apart, spilling their contents into nearby tissue. The mystery of stroke is how and why cells in the surrounding area die off hours or days later. This delayed, or secondary, brain damage is now considered potentially preventable. A growing body of research suggests that the focus of both primary and secondary stroke damage—and potential stroke therapy—lies in the mitochondria.

While the brain consumes a disproportionate share of the body’s circulation (14%) and oxygen (20%), its energy reserves are very small, especially considering the brain’s extraordinary energy demand. Other cells with high energy demand, such as muscle cells, are much better equipped to generate energy from stored glucose. The brain’s energy stores can sustain metabolism for only about one minute. Hence neurons are particularly vulnerable when cellular respiration fails during ischemia (reduced blood flow). It is no wonder that the mitochondria are considered “subcellular targets” of ischemic injury in the brain. As summarized in one research paper (Veitch K et al., 1992):

Indeed, the transition from reversible to irreversible ischemia has been suggested to depend on the functional state of mitochondria... restoration of oxidative metabolism [the energy-producing cellular respiration process] determines functional recovery.

Brain mitochondria, with their special sensitivity to reduced blood flow, exhibit the first signs of brain injury during ischemia. Even a moderate reduction of cerebral blood flow substantially impairs cellular respiratory activity. Injury to mitochondria during and after a stroke brings manifold consequences. These include metabolic failure, oxidative stress, calcium dysregulation, increased excitotoxicity and promotion of programmed cell death. The effects of mitochondrial impairment cause further mitochondrial impairment, generating “a vicious cycle of subcellular injury and abnormal intracellular conditions” in the aftermath of a stroke (Fiskum G et al., 1999).

Mitochondria may actually suffer greater injury when blood flow is reduced than when it stops completely. This is because complete cessation of blood flow also cuts off the supply of oxygen, thereby reducing oxidative stress. When blood flow is merely reduced, oxygen continues to flow, generating free radicals on top of those spewed out by stroke-impaired cellular respiration. These radicals attack mitochondrial lipids, DNA, and respiratory chain components. The return of blood and oxygen to the affected area likewise does greater injury to the cellular respiratory chain after a reduction in blood flow than after a complete cutoff.

The scope of the neurological impairment caused by a stroke depends upon secondary brain damage, also called delayed neuronal death. Research suggests that secondary brain damage follows from secondary mitochondrial and bioenergetic failure after blood flow resumes.

The cascade is set in motion by the failure of cellular respiration and associated ATP production, which leads to depletion of cellular energy stores. This slows and then stops the cellular sodium/potassium pump. Cell membranes lose their electrical polarity. As calcium regulation fails, mitochondria become overloaded with calcium. Glutamate levels rise, triggering excitotoxicity. This in turn aggravates calcium influx into cells, activating enzyme systems that break down cellular structures.

During the ischemic cascade brain cells are particularly vulnerable to oxidative assault since part of the cellular antioxidant defense system (SOD, or superoxide dismutase) is compromised during ischemia. There are many sources of oxidative stress during stroke, including increased production of superoxide and nitric oxide, which combine to form the neurotoxin peroxynitrite.

The eventual return of blood and oxygen raises oxidative stress levels higher still and may lead to secondary bioenergetic failure. Immune and inflammatory cells contribute to delayed oxidative stress. In energetically strained cells overloaded with calcium the mitochondrial megachannels open, leading to cell death.

While there have been few studies thus far on CoQ10 in cerebral ischemia, its protective effect upon the heart has been demonstrated in many studies of myocardial ischemia and reperfusion (interruption and return of blood flow to the heart). These studies suggest that CoQ10 protects against changes in heart structure and function caused by ischemia and reperfusion. CoQ10 pretreatment prior to ischemia reduces depletion of ATP, the molecule that stores the energy produced by cellular respiration, while preventing calcium overload.

One of the ways CoQ10 helps maintain bioenergetic function in the ischemic

The question of whether secondary brain damage occurs through necrosis or programmed cell death—or something in between—is one of the most hotly debated issues in medical research today. Much recent evidence points to programmed cell death as a major factor in delayed neuronal death. While this cellular suicide program disposes of cells in a neat, orderly way, stroke may trigger it accidentally. Mitochondrial conditions during and after ischemia appear to set off the suicide program in otherwise viable cells. Whatever the mode of cell death, similar processes of cellular energy failure, consequent calcium overload and excitotoxicity, oxidative stress and opening of the mitochondrial megachannel may unfold.

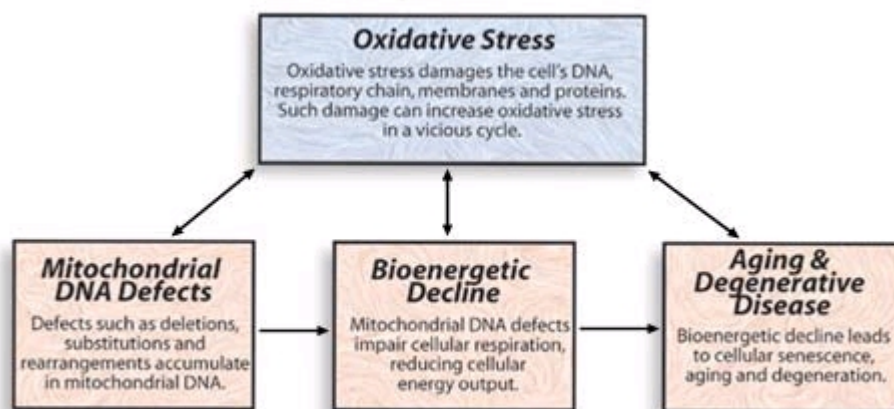
heart is through an enzyme called creatine kinase. This enzyme is crucial to energy metabolism but is exquisitely sensitive to oxidative stress. Creatine kinase is often inactivated by free radicals during reperfusion, the reflow of blood following ischemia. CoQ10 helps protect creatine kinase during reperfusion, an example of how CoQ10's antioxidant action supports cellular energy production.

Measures that support cellular energy production and antioxidant defense while protecting against excitotoxic damage and programmed cell death might help protect this tissue. CoQ10's properties would appear to lend themselves to this, and animal experiments with CoQ10 support this hypothesis. Japanese scientists tested CoQ10 in a standard animal model of human stroke. They induced strokes in Mongolian gerbils by blocking the carotid artery. The gerbils that developed stroke symptoms were either left untreated, or treated after four hours with subcutaneous pellets of CoQ10 or one of two drugs. The untreated gerbils lived 17 hours on average, and all were dead after 28 hours. In contrast to this, nearly half (45%) of the gerbils treated with CoQ10 survived until the end of the experiment four weeks later. The two drugs tested were far less successful than CoQ10 in prolonging the lives of the gerbils following stroke.

A model of bioenergetic aging

The bioenergetic theory of aging was first proposed by Australian scientist Anthony Linnane in 1989 (see "Bioenergetic Therapy for Aging," February 2001, p. 24). According to this theory, mutations accumulate in mitochondrial DNA with age, leading to a decline in cellular energy production. This bioenergetic decline results in degenerative disease and old age frailty.

Mitochondrial DNA and cellular respiration are highly susceptible to oxidative damage, which in turn generates additional oxidative stress. CoQ10 enhances cellular energy production while helping to protect mitochondrial DNA and the cellular respiratory chain from oxidative damage.



The series of boxes below shows how mitochondrial deterioration can hasten aging and degeneration, as proposed by Linnane. Mitochondria are highly susceptible to oxidative stress, which reinforces the other factors.

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Vasoconstriction and vasospasm

A new study on endothelins reveals some of the mechanisms through which CoQ10 may exert neuroprotective effects. Endothelins are potent vasoconstrictors found in the body. Ongoing research implicates them in a host of vascular disorders contributing to hypertension, atherosclerosis, congestive heart failure and kidney failure, and evidence is mounting of their involvement in stroke. When endothelins are injected into the brains of animals, the result is cellular energy decline, acidosis, excitotoxicity, depletion of cellular antioxidants, and eventually the collapse of brain cell metabolism. However, when CoQ10 was administered prior to injection of the endothelins, it protected the antioxidant defenses of brain cells and restored them to normal metabolic function. In particular, CoQ10 exerted a marked sparing effect on the key cellular antioxidants glutathione and superoxide dismutase (SOD), and normalized cellular energy production (ATP) and lactate levels (acidosis) in 24 hours.

Endothelins play a particularly important role in cerebral vasospasm. About 2% of adults have aneurysms, a balloon-like deformation in cerebral blood vessels. When an aneurysm ruptures, the two out of three patients who survive the initial cerebral hemorrhage face several possible complications. The most common serious complication is "second stroke," the cerebral vasospasm. This is a prolonged narrowing of a blood vessel that causes ischemia in the downstream brain tissue.

Researchers at the Polish Academy of Sciences Medical Research Center tested the protective effect of CoQ10 in a rabbit model of cerebral vasospasm. They blocked arteries to reduce cerebral blood supply and later injected blood into the brain to simulate hemorrhage. Following the injection, one group of rabbits was given CoQ10 orally three times a day while the other group was left untreated. All of the untreated rabbits displayed significant neurological deficits (Grade 3 or 4) or died. None of the rabbits given CoQ10 displayed a noticeable neurological deficit, and all of them survived. Microscopic examination revealed no lesions in the brain tissue of the CoQ10 treated group, whereas multiple lesions "suggestive of degeneration or disappearance of neurons... and of myelin disintegration" were found in brain tissue from the untreated rabbits (Grieb P et al., 1997).

The underlying causes of cerebrovascular disease suggest that CoQ10 may have a preventive effect. Most cerebrovascular disease results from atherosclerosis or hypertension. Atherosclerosis narrows blood vessels in the brain, making it easier for blockages to develop; dislodged atherosclerotic plaque can itself cause blockages. Hypertension is the most common cause of hemorrhagic stroke. As discussed earlier in this series, CoQ10 helps protect against the oxidative damage that leads to atherosclerosis, and may aid in controlling blood pressure. Animal studies suggest that CoQ helps reverse age-related loss of arterial tone, which contributes to both cerebrovascular and cardiovascular disease. And of course CoQ10 plays a unique role in sustaining brain bioenergetics. While the potential of CoQ10 in stroke prevention and treatment appears promising, we can only hope that clinical trials will soon be undertaken to test this proposition.

Stroke may mimic long-term genetic effects of aging. Research in mice recently found that stroke causes some of the same mitochondrial DNA deletions associated with aging. The researchers speculate that there could be a single mechanism at work, however much further research is needed before stroke research can be meaningfully applied to brain aging.

The politics of CoQ10

If CoQ10 were as ubiquitous in American households as it is in the cells of the body, there is little doubt that public health would benefit. Why isn't CoQ10 as popular here as in Japan, where it is one of the top half dozen prescription medicines? CoQ10 researcher Peter Langsjoen (1994) answered a similar question this way:

The answer to this question is found in the fields of politics and marketing and not in the fields of science or medicine. The controversy surrounding CoQ10 likewise is political and economic, as the previous 30 years of research on CoQ10 have been remarkably consistent and free of major controversy. Although it is not the first time that a fundamental and clinically important discovery has come about without the backing of a pharmaceutical company, it is the first such discovery to so radically alter how we as physicians must view disease. While the pharmaceutical industry does a good job at physician and patient education on their new products, the distributors of CoQ10 are not as effective at this. This education is very costly and can only be done with the reasonable expectation of patent protected profit.

Langsjoen's point concerning education is well taken, inasmuch as CoQ10 cuts across conventional diagnostic and therapeutic categories. Systemic bioenergetic therapy is not yet on the horizon of conventional medicine.

The “Not Invented Here” syndrome may also play a part in making CoQ10 unwelcome to the American medical establishment. It was Japanese industry that developed the complex fermentation process used to grow natural CoQ10. To this day, all pharmaceutical grade CoQ10 comes from Japan. In the sixties and seventies, when mainstream medicine in the U.S. was yet more resistant to nutritional therapies than it is today, it was Japanese and European scientists who demonstrated the therapeutic effectiveness of CoQ10. Ironically, CoQ10 was invented here —American scientists discovered and first synthesized CoQ10 in the fifties.

What is most unpalatable of all to the U.S. pharmaceutical-medical establishment is that CoQ10 can neither be patented nor regulated as a drug. In fact, it is widely available as a nutritional supplement. U.S. pharmaceutical companies have nothing to gain by promoting or testing this expensive import, for which there is no domestic manufacturing infrastructure. It would cost billions of dollars to conduct the massive clinical trials that drugs undergo in all the potential areas of CoQ10 application. When the medical establishment does embrace CoQ10 it may be in the form of a patentable synthetic analogue (such as idebedone).



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Mitochondrial and Neuromuscular Diseases

Since the discovery of the first genetic disease of the mitochondria in 1988, the number of recognized mitochondrial diseases has ballooned. These diseases present extraordinarily complicated genetic and clinical pictures that cut across established diagnostic categories. They primarily affect the brain, nerve, muscle, heart, kidney and endocrine system, whose high energy requirements can no longer be fully met. In addition, a wide range of degenerative diseases have been found to involve one or more of hundreds of known mitochondrial mutations.

Patients with genetic CoQ10 deficiency may suffer dysfunctions in brain, nerve and muscle, often including exertional fatigue and seizures. Such patients appear to respond to CoQ10 supplementation, but observations are limited since diagnosis of this disorder is in its infancy. CoQ10 deficiency is one of the mitochondrial diseases caused by mutations in non-mitochondrial DNA, that is DNA in the cell nucleus.

Case reports and pilot studies have found that some patients with mitochondrial diseases respond to long-term CoQ10 therapy. For example, promising results have been reported in MELAS, Kearns-Sayre syndrome and maternally inherited diabetes with deafness. An Italian study demonstrated the impact of CoQ10 therapy on the living tissue of six patients with mitochondrial cytopathies. They measured the bioenergetic activity in the brain and skeletal muscle of the patients using high-technology diagnostic equipment (phosphorus magnetic resonance spectroscopy). After six months of CoQ10 therapy at 150 mg per day, brain bioenergetics returned to normal in all patients, and skeletal muscle energetics improved significantly. A new study applies this diagnostic technology to Friedrich's Ataxia, which is characterized by a deficiency of a mitochondrial protein called frataxin recently discovered to activate cellular respiration. The study found that supplementation with CoQ10 plus vitamin E brought a “dramatic improvement of cardiac and skeletal muscle bioenergetics. . . after only three months of therapy” (Lodi R et al., 2001). A just-published study of familial ataxias with no known genetic cause reports that CoQ10 supplementation improved patients' scores by 25% on a scale measuring balance, speech and movement. The five patients who could not walk at the beginning of the trial were able to walk with some assistance after supplementation (dose levels varied).

Since all cells (except red blood cells) contain mitochondria, mitochondrial diseases tend to affect multiple body systems. Of course some organs and tissues depend more than others upon the energy the mitochondria produce.

At the genetic level, the picture is more complex. The level of inherited mitochondrial DNA defects may establish an individual's “bioenergetic baseline.” As additional mitochondrial DNA defects develop over the course of a lifetime, bioenergetic capacity may decline until thresholds are crossed where organs malfunction or become susceptible to degeneration.

Another genetic complication is that each mitochondrion contains many copies of mitochondrial DNA, and each cell and tissue contains many mitochondria. At both these levels, there may be many different defects in different copies of the mitochondrial genome. This is especially true of the defects that cause clinical pathologies.

For a particular tissue or organ to become dysfunctional, a critical number of its mitochondrial DNA's must be mutated. This is called the “threshold effect.” Each organ or tissue is more susceptible to some mutations than others and has its own particular mutational threshold, energy requirement and sensitivity to oxidative stress. All these factors combine to

determine how it will respond to genetic damage. The picture is further complicated by interactions between DNA in mitochondria and in the cell nucleus. The result is that the same mitochondrial DNA mutations can produce remarkably different symptoms in members of the same family, while different mutations can produce the same symptoms.

Some of the specific mitochondrial mutations found in mitochondrial diseases develop spontaneously in the aged. More generally, the picture we have sketched of mitochondrial disease illuminates the consequences of Linnane's theory: it helps explain how mitochondrial mutation-driven bioenergetic decline can have such varied and complex effects over the course of aging.

There is a heterogeneous group of neuromuscular disorders whose exact cause and effective treatment remain largely unknown. These include muscular dystrophy, some encephalomyopathies and various neurogenic atrophies. Several small trials and case reports suggest that some patients with these diseases respond to CoQ10 therapy.

CoQ10 pioneer Karl Folkers observed that cardiovascular disorders are associated with these conditions, as might be expected if cellular energy production were impaired. He therefore conducted a double-blind trial to assess the effect of CoQ10 on cardiac performance in patients with muscular dystrophies and neurogenic atrophies. After three months of treatment with 100 mg of CoQ10 per day, cardiac function was significantly improved in all patients and half the patients showed distinct improvement in movement and exercise capacity. Folkers hypothesized that these conditions have in common a deficiency of CoQ10.

By the same token, mitochondrial defects may contribute to heart disease in some patients. A recent study of dilated cardiomyopathy found that about one in four patients had pathological mutations in the mitochondrial DNA of heart tissue.

Conclusion

In this series of articles we have explored fundamental life processes—cellular bioenergetics, antioxidant defense, mitochondrial genetics—intertwined with mechanisms of aging and degeneration. It will take many years before these biomedical research frontiers revolutionize the practice of conventional medicine. A common theme running through our exploration has been CoQ10's unique point of leverage on these life processes. Insofar as health—and aging—begins in the cell, CoQ10 may be a cornerstone of vitality and longevity.

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