

**BASIC SCIENCE ASPECTS OF THE MITOCHONDRIA
SECTION VIII**

DRUGS, CHEMICALS AND MITOCHONDRIA

Maternally inherited and acquired defects in mitochondrial function are now known to cause most of the common diseases of ageing, including Type II Diabetes Mellitus, Atherosclerotic Heart Disease, Stroke, Cancer, Alzheimer's Disease, and Parkinson's Disease. In all of these the function of mitochondria is markedly disturbed, and energy production declines to a critical level below which inherited or acquired mitochondrial errors express themselves.

In 1995, the entire program of the 25th Annual Meeting of the American Ageing Commission and the American College of Clinical Gerontology was directed to the role of mitochondria in the Chronic Diseases of Ageing.

Despite this, most physicians in America are not yet aware of the clear connection between these diseases and abnormalities in mitochondrial function, nor are they aware of the pivotal role their use of blocking and inhibiting drugs has had on creating the disturbances in mitochondrial function which leads to the appearance of these latter disorders.

The diseases of ageing outnumber mitochondrial diseases in children about 5,000 to 1 according to the directors of the Mitochondrial and Metabolic Disease Center at the University of California, San Diego. The chronic degenerative diseases of aging are due in part to the fact that most of the sufferers have been exposed for 20 to 30 years to a host of environmental and toxic pollutants which increase the risk for these diseases. Studying the mitochondrial diseases of children has shed some considerable light on the causes and may lead to the development of effective treatment and preventive strategies of the adult onset degenerative diseases.

The first convincing clue that environmental toxins may cause Parkinsonism came from some young drug users who developed neurological symptoms closely resembling Parkinson's disease. The physicians in the San Francisco Bay area were puzzled that all these patients with Parkinson's like symptoms were too young to have clinical symptoms usually seen in the elderly with Parkinson's disease. Investigating the causes of the neurological symptoms, led to the discovery that all the young patients were drug (heroin) addicts and that their neurological symptoms could be relieved by L-DOPA treatment. Postmortem examination of one of the patients who died of drug overdose showed that the agent which produced Parkinson-like symptoms was a contaminant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the drug preparation. Further studies showed that MPTP produced Parkinson-like symptoms in monkeys similar to those in humans, and from the demonstration that MPTP disrupts mitochondrial energy metabolism, damages the substantia nigra, and induces Parkinsonism in humans. The active and neurotoxic metabolite of MPTP is MPP⁺ which is formed in the body by the action of glial monoamine oxidaseB. MPP⁺ is then selectively transported via dopamine transporter into nigrostriatal dopaminergic neurons, where it inhibits mitochondrial complex I, depletes ATP and causes neurodegeneration by an unknown mechanism. Mitochondrial energy deficit is the primary cause of MPTP/MPP⁺ neurotoxicity. Some studies have shown that MPP⁺ interacts with mitochondrial complex I, produces free radicals, and causes an irreversible inactivation of complex I enzyme activity. Other studies have shown that nitric oxide mediates MPTP neurotoxicity which can be blocked by 7-nitroindazole, a potent inhibitor of neuronal nitric oxide synthase (NOS). It has also been demonstrated that mice lacking the NOS gene are refractory to MPTP neurotoxicity. A number of investigators have suggested that NMDA receptors play a crucial role in MPTP/MPP⁺

neurotoxicity, which can be blocked by NMDA receptor antagonists. Some investigators, however, failed to observe the protective effect of NMDA receptor antagonists against MPTP/MPP+ neurotoxicity.

3-Nitropropionate (3-NPA) is widely distributed in toxic plants such as *Astragalus* species and was identified in 1954 as the component of *Indigofera endecaphylla Jacq* responsible for its toxicity to domestic animals. 3-NPA is also produced by the fungus *Arthrinium spp* which was responsible for the development of an acute encephalopathy in Chinese children. Magnetic Resonance Imaging (MRI) of affected individuals showed a bilateral necrosis of the putamen with delayed dystonia in some patients. 3-NPA produces basal ganglia degeneration and extrapyramidal symptoms in humans and in experimental animals. Some investigators have reported age-dependent vulnerability of striatal neurons following intrastriatal, subacute, or chronic administration of 3-NPA in rats. Some investigators studied neurochemical and histologic changes following intrastriatal injection of 3-NPA, others investigated locomotor changes and striatal lesions in 3-NPA treated rats. One group of investigators observed axonal degeneration in the caudate-putamen region of rats treated with 3-NPA. Pretreatment with nerve growth factor, prior decortication, or treatment with glutamate antagonists was able to block the toxic effect of 3-NPA.

The chemical structure of 3-NPA is isoelectronic with succinate; 3-NPA acts as a suicide inhibitor of succinic dehydrogenase, an enzyme of citric acid cycle and a component of mitochondrial complex II. 3-NPA reduces energy supplies of cultured cortical explants and causes neuronal degeneration by an excitotoxic mechanisms. It has been demonstrated that noninvasive spectroscopic imaging can be used to detect neurochemical alterations induced by 3-NPA. Exposure of cultured striatal or cortical neurons to 3-NPA has shown that neuronal cell death

occurs by an apoptotic mechanism.

Studies have shown that 3-NPA decreases synaptosomal respiration in a concentration-dependent manner, and it was reported that the earliest sign of impairment of energy metabolism was a fall in the ratio of phosphocreatine/creatine. In the initial phase of intoxication, 3-NPA selectively inhibits tricarboxylic acid cycle (TCA) of GABAergic neurons; glial TCA cycle remained unaffected during this time. These studies explain why the caudate/ putamen neurons, which are GABAergic, are selectively damaged by 3-NPA. Other studies have suggested that an impairment of energy metabolism by 3-NPA may underlie neuronal death by an excitotoxic mechanisms in laboratory rats. They have provided in vivo evidence for the involvement of free radicals in excitotoxic death of neurons and shown that 3-NPA toxicity was significantly attenuated in copper/zinc superoxide dismutase transgenic mice. It was suggested that both bioenergetic and oxidative stress play an important role in neurodegenerative diseases.

Recent work has shown that chronic exposure to 3-NPA replicates the cognitive and motor deficits and behavioral pathology of Huntington's disease, in baboons and rats, respectively. It has been suggested that treatment of rodents and primates with 3-NPA provides a good animal model of HD. Treatment of animals with Q10 and nicotinamide, agents that improve oxidative phosphorylation and quench free radicals, ameliorate striatal lesions. The combination of NMDA receptor antagonist, MK-801, with coenzyme Q10 was found to be a more effective treatment for protecting neurons.

Potassium cyanide is one of the most toxic occupational and environmental chemicals. Humans get exposed to toxic levels of cyanide from consumption of cyanophoric plants (e.g., cassava), from tobacco smoke, from alkyl-cyanides used as solvents, from cyanide salts used for

polishing and metal cleaning, and the antihypertensive drug sodium nitroprusside. The primary target organ of cyanide is the central nervous system. Cyanide rapidly inhibits COX activity, lowers energy supplies and causes neurological dysfunction within seconds. Cyanide exposure also causes neuronal degeneration in brain and produces progressive parkinsonism and dystonia. Magnetic resonance imaging (MRI) shows bilateral lesions of the basal ganglia. Positron emission tomography (PET) with 6-fluoro-L-dopa revealed marked dysfunction of dopaminergic transmission similar to that observed in parkinsonism. Chronic cyanide exposure has been associated with motor neuron disease. Cyanide depletes gamma aminobutyric acid and elevates glutamate concentrations in brain. Dopaminergic system of rodents is highly susceptible to cyanide neurotoxicity. Studies have suggested that cyanide selectively affects basal ganglia by an excitotoxic mechanism following disruption of energy metabolism. The role of COX inhibition as the primary biochemical lesion in cyanide toxicity is unresolved. It has been shown that cyanide rapidly depresses synaptic transmission without inhibiting COX activity.

Cyanide increases cytosolic free Ca^{2+} in energy-compromised neurons by the activation of NMDA receptors and initiates a series of intracellular cascades which culminate in cell death. In PC12 cells, cyanide activates phospholipase A2, stimulates generation of inositol triphosphate through an interaction with the glutamate/ metabotropic receptors and induces an apoptotic cell death. The toxic effect of cyanide can be blocked with NMDA receptor antagonists. Cyanide inhibits brain catalase, superoxide dismutase, and glutathione peroxidase and increases lipid peroxidation in the striatum. Studies suggest that oxidative stress plays an important role in the expression of CN neurotoxicity.

In parts of Africa, where cassava consumption is high and protein intake is low, cyanide is

etiologically implicated in causing neurodegenerative diseases, tropical ataxic neuropathy and konzo, a paralytic disorder characterized by spastic paraparesis. Populations subsisting on a low protein diet on a chronic basis, are good candidates for developing neurological diseases. Cassava harbors a cyanogenic glucoside, linamarin, which liberates cyanide, a potent inhibitor of COX activity. There are two defense mechanisms against cyanide toxicity. First, cyanide is rapidly, but reversibly, trapped by methemoglobin to form cyanomethemoglobin. Second, additional cyanide is detoxified to thiocyanate (SCN⁻) by the enzyme rhodanese. This mechanism requires sulfane sulfur substrates derived from dietary sulfur amino acids, cysteine and methionine. In protein-deficient individuals, where sulfur amino acid concentrations are low, detoxification of cyanide to SCN⁻ may be impaired and cyanide may be metabolized to neurotoxic cyanate (OCN). Recent work has shown that OCN inhibits COX activity, uncouples oxidative phosphorylation, and blocks the activity of glutathione reductase and reduces glutathione in rodent brain.

Sodium azide is very reactive toxic chemical which is rapidly converted to volatile hydrazoic acid. Sodium azide is extensively used as a herbicide, fungicide, insecticide, and in inflatable “air bags” in automobiles and emergency escape chutes for aircraft. Sodium azide is a potent inhibitor of COX activity of the mitochondrial respiratory chain and may deplete energy supplies in certain brain regions. COX inhibition may lead to increased free radical (azidyl and hydroxyl) formation by the mitochondria. Chronic and continuous administration of sodium azide in rats impairs learning, and produces memory deficit. Evidence is accumulating that the toxic effects of NaN₃ (such as convulsive seizures) may be due to its conversion to nitric oxide. Acute or chronic exposure with NaN₃ produces pathological lesions in substantia nigra, a brain area commonly affected in parkinsonism. Demyelination, necrosis of the optic nerves, caudate nucleus,

and putamen are common in monkeys treated with repeated doses of NaN₃. Recent work has shown that NaN₃ causes striatal damage by an excitotoxic mechanism following energy depletion.

Carbon monoxide is a highly poisonous, odorless, colorless, and tasteless gas. It is an ubiquitous environmental pollutant produced by partial oxidation of hydrocarbons from natural gas or by the gasification of coal. Fuel combustion in areas of limited ventilation is a common cause of acute CO poisoning. CO combines with the hemoglobin of the blood to form carboxyhemoglobin and thereby blocks its oxygen binding/carrying properties. CO exposure blocks ATP generation, by inhibiting COX activity of the mitochondrial electron transport chain, and causes severe extrapyramidal degeneration. The toxic symptoms of CO poisoning may include dizziness, convulsions, coma, respiratory failure and death. Humans with CO poisoning develop parkinsonism six weeks postexposure. The pathological changes produced in the brain by CO are similar those seen in hypoxia-ischemia. Bilateral necrotic lesions of the globus pallidus are recognized as a hallmark of CO poisoning.

Manganese (Mn) is an essential element required for the maintenance of normal health, but it causes neurotoxicity in rodents, monkeys and humans. In mining workers, acute intoxication with Mn causes speech impairment, irritability and hallucinations. Human exposure to Mn occurs through use of potassium permanganate, a powerful oxidizing agent. Manganese is widely used as a fungicide in agriculture, where workers develop neurological signs of parkinsonism and dystonia. Neuropathological lesions in Mn poisoning are found in substantia nigra, globus pallidus, caudate nucleus, and putamen. Decreased dopamine levels are found in the striatum of humans, primates and rodents. Evidence has been provided that both divalent and trivalent manganese produce reactive oxygen species. Manganese preferentially accumulates in mitochondria, and causes

neuronal degeneration by an excitotoxic mechanism secondary to inhibition of cerebral oxidative energy metabolism.

Mercury occurs in the environment as an element and in inorganic and organic compounds. Many humans are continuously exposed to minute concentrations of inorganic and organic mercury through mercury-amalgam dental work. Since the outbreak of Minamata disease following mercury poisoning in Japan, extensive studies of the pathological and clinical changes in affected patients have been performed. Mercury and its compounds disrupt protein synthesis and energy transformation. Alkyl mercurials affect synaptosomal respiration and perturb citric acid cycle and mitochondrial electron transport chain. The predominant pathological changes occur in the cerebral cortex, but granule cells and basal ganglia are also affected. Mercury intoxicated subjects display parkinsonian features, rigidity, tremors, ataxia, impairment of speech, and memory deficit. Subcellular distribution studies have shown that Hg preferentially binds to the mitochondria and microsomes.

Despite a long history of lead poisoning, the precise mechanism of its neurotoxicity is unknown. Lead has neurotoxic effects on both central and peripheral tissue. Exposure to lead has greater toxic effects on the nervous systems of children than adults. In addition to neurotransmitter changes, lead affects energy metabolism before neuropathologic changes. Lead interacts with magnesium in the mitochondria and thereby affects oxidative phosphorylation. It has been reported that neonatal exposure of rats to low levels of Pb produces changes in phosphorylation activity in brain mitochondria. Relatively high concentrations of lead are required to inhibit mitochondrial respiration in the cerebellum.

In a significant proportion of patients with Acquired Immuno-deficiency Syndrome

myopathy has been observed in those receiving the anti-viral agent AZT (3'-Azido-3'-deoxythymidine), and this is often reversed if AZT treatment is suspended. Some of the reported clinical features observed in patients with AZT-induced myopathy include lactic acidosis, myalgia, muscle weakness and abnormal skeletal muscle mitochondria (i.e., ragged-red fibres). Such features are typical of mitochondrial myopathy, except that AZT-induced myopathic patients have elevated serum creatine kinase levels. Examination of mitochondrial respiratory complexes revealed reduced activities of succinate cytochrome-*c*-oxidase and cytochrome-*c*-oxidase. Mitochondrial DNA content was lower in patients with AZT-induced myopathy, presumably due to the inhibition of mitochondrial γ -DNA polymerase by AZT.

When dosed at relatively high levels of AZT (50-100 mg/kg body weight per day) for extended periods (35-70 days), animals developed mitochondrial abnormalities in cardiac and skeletal muscle, weight loss, elevated serum creatine kinase and lactic acidosis. Histological studies revealed ragged-red fibres in skeletal muscle and mitochondrial proliferation of abnormal morphology in skeletal and cardiac muscle tissues in which the highest levels of AZT were found. Isolated skeletal muscle mitochondria from treated animals had impaired Complex I and II activities. Interestingly, brain mitochondria were unaffected, perhaps reflecting the biodistribution of AZT, where brain tissue contained less than 20% of the AZT content of skeletal muscle. It was concluded from these studies that AZT, as a consequence of its inhibition of mitochondrial γ -DNA polymerase, is a mitochondrial toxin affecting Complexes I and II.

In his chapter on Defects in mitochondrial function, in V. Darley-Usmar and A.H.V. Schapira (Eds), Chapel Hill and London, Portland Press (1994), "Mitochondria: DNA, Proteins

and Disease", David John Hayes lists the following drugs reported to cause mitochondrial dysfunction:

<u>Agent</u>	<u>Use/Action</u>	<u>Abnormalities</u>
DPI	Complex I Inhibitor	Reduced oxidative enzymes, muscle fatigue
Antimycin A.	Complex III Inhibitor	Swelling/disruption of mitochondria
Oligomycin	Complex V Inhibitor	Swelling/disruption of mitochondria
Fluoroacetate	Citric acid cycle inhibitor	Ultrastructural, reduced oxygen uptake
Crotoxin	Snake venom	Ragged-red fibres, ultrastructural
Prenylamine	Vasodilator	Reduced oxygen uptake, inhibition of calcium transport
Bayer K 8644	Calcium channel agonist	Ultrastructural
Germanium (GeO ₂)	Trace element	Ragged-red fibres, ultrastructural
Zidovudine (AZT)	Antiviral	Ragged-red fibres, reduced oxygen uptake, ultrastructural
Clofibrate	Lipid lowering	Ultrastructural, CoQ deficiency?
Statines		
Lovastati		
Cyclosporin	Immune suppression	Ultrastructural
Emetine	Amoebiasis/vomiting induction used chronically by anorexics	Ultrastructural, reduced oxidative enzymes

Neurons have an absolute dependence on a continuous supply of ATP to support ion pumps in excitable and synaptic membranes, intracellular neuronal and axonal transport, neurotransmission, and the synthesis of energy requiring enzyme systems. A plethora of scientific evidence supports the notion that the rate and duration of energy deficit plays a major role in dictating the distribution and pattern of neurodegeneration. Neuronal peikarya with glutamatergic inputs, such as the striatum, hippocampus and substantia nigra, are especially vulnerable to an abrupt and severe toxin-induced decline in energy status through an excitotoxic mechanism. For example complex I inhibition by methyl phenyl pyridinium ion (MPP⁺), complex II inhibition by 3-NPA and malonate, complex IV (COX) inhibition by cyanide, causes selective neuronal degeneration in the brain. Sodium azide that inhibits COX activity, induces excitotoxic striatal

damage. Complex V inhibition by cyanate, which uncouples the strict relationship between electron transport and oxidative phosphorylation, inhibits brain COX activity both in vitro and in vivo, and causes striatal and motor neuron degeneration. Mild energy depression of chemical energy produced by the inhibition of the glycolysis-citric acid cycle or attenuation (rather than blockade) of mitochondria electron transport chain compromises the delivery of materials via axonal transport and causes primary distal axonal degeneration. Disruption of energy metabolism initiates a vicious cycle of biochemical events that culminates in neurodegeneration.

Similar processes, less immediately discernible than those in the nervous system take place in the cells, tissues, and organs of other systems which are subjected to chemicals which have the property of uncoupling oxidative phosphorylation or otherwise interfering with mitochondrial function in the heart, liver, kidneys, lungs, pancreas or muscles. Such chemicals may be environmental pollutants or may well be pharmaceuticals which have the property of blocking or inhibiting bodily processes.

Until the cultural gap between science and its assimilation into the medical education system closes, the facts of mitochondrial diseases and conditions will remain more of a mystery to the allopathic medical profession than the dark side of the moon and it will remain a part of the problem rather than the solution.

One of the bad mistakes we may have been making is the indiscriminate use of drugs to treat such diseases, because it is beginning to appear that many drugs also have the property of interfering with the ability of the mitochondria to make ATP although there is enough fuel and oxygen available for that purpose.

Although interference with mitochondrial function is the way in which many synthetic pharmaceuticals create subtle and long-term toxicity and unwanted side effects at this time, drugs are not tested nor are required to be tested to determine whether or not they have the property of interfering with the ability of mitochondria to produce ATP.

Many modern pharmaceuticals achieve their effect by blocking or inhibiting some biological process. For instance Prozac and Luvox are selective serotonin re-uptake inhibitors and antibiotics inhibit the metabolic processes of bacteria.

There is a trend in pharmacology to select drugs which block or inhibit some physiological

process or biochemical event. A few examples should suffice to illustrate this:

Selegiline (Eldepryl): Mechanism of Action: Potent monoamine oxidase (MAO) type-B inhibitor; may also increase dopaminergic activity by interfering with dopamine reuptake at the synapse.

Sertraline (Zoloft): Mechanism of Action: Selective inhibitory effect on presynaptic serotonin reuptake.

Sibutramine (Meridia): Mechanism of Action: Blocks the neuronal uptake of norepinephrine and serotonin and to a lesser extent, dopamine.

Simvastatin (Zocor): Mechanism of Action: competitively inhibiting the enzyme that catalyzes the reduction of HMG CoA reductase

Sparfloxacin (Zagam): Mechanism of Action: Inhibits DNA-gyrase; inhibits relaxation of supercoiled DNA and promotes breakage of double stranded DNA.

Tetracycline (Achromycin, achromycin V, Ala-Tet, Nor-Tet, Panmycin, Robitet, Sumycin, Teline, Tetracycl, Tetralan, Topicycline): Mechanism of Action: Inhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria; may also cause alterations in the cytoplasmic membrane.

This list might easily be made pages long, but these few examples should suffice to illustrate.

While mitochondria have their own DNA, they are also dependant to a large extent on the cells nuclear DNA to produce proteins, which they use.

While some mitochondrial disorders are due to intramitochondrial events, many others are dependent on both mitochondrial and nuclear DNA so the function of mitochondrion can be vulnerable to chemicals which inhibit either mtDNA, NDNA, or both.

Persons suffering from a Chronic Degenerative Disease should be thoroughly evaluated to determine what prescription drugs they ingest, what over-the-counter drugs they ingest and what recreational drugs they ingest as well as how much of their diet contains chemicals which are capable of interfering with the function of mitochondria and the production of ATP in sufficient quantities to maintain health. Unless such ingestion is stopped, there will be little possibility of reversing these diseases.

In antibiotic use, chemicals, which inhibit the life processes of bacteria, inhibit the life processes of all bacterium, including several which are essential to health such as the gut flora and also the mitochondria which are bacterial symbionts.

There are circumstances in which the administration of antibiotics are essential to save lives and such use is justified, but even then, these should be administered in such a way as to minimize their impact on non-pathogenic and essential bacteria.

It is common practice to administer antibiotics orally, in which case the bacterium, which make up the useful gut flora are harmed along with the pathogenic bacteria. The life saving therapy should be administered by injection rather than orally in order to avoid dysbiosis.

Much of the damage from the indiscriminate over-use of antibiotics has been done over the past 50 years has resulted in both the widespread development of antibiotic resistance, as well as the severe impairment of gut ecology in people who have received oral antibiotics for every conceivable indication. Antibiotics have no effect on viruses and are of no use in the treatment of viral disease, but they have been used to treat viral diseases routinely, because they were regarded as panaceas.

To the Allopathic mind, as well as to the regulatory agencies, toxicity to be appreciated, must be immediate; apparent within a day or week or it is ignored; long term toxicity is simply not considered or even thought of until months or years later, when it results in serious impairment or failure of some organ, frequently the liver.

Much the same is true of the thousands of synthetic compounds routinely added to processed foods to extend their shelf life.

In the race to develop new and patentable molecules and get them to market, long-term toxicity is ignored or information indicating its presence is suppressed and denied by the proponents of the clinical usefulness of the new molecule.

For the past two centuries, thoughtful people have been warning that the use of toxic substances as drugs is ultimately harmful. Samuel Hahnemann's polemics are well known. During the Civil War a Dr. R. T. Troll gave an address at the Smithsonian Institute, attended by President Lincoln and a number of Government officials in which he commented that the allopathic drug treatments then predominant and taught in medical schools were "active in philosophy, abysmal in

science, in opposition to nature and in direct conflict with every law of the vital organism, and that it's application to cure of diseases and the preservation of health is uncertain, dangerous and often fatal and, on the whole, vastly more injurious than useful, pointing out that in the treatment of sicknesses patients receiving no medicine did better than those who did.” A Century later, the National Institute of Environmental Health Science in a large seminar on the Biological Relevance of Immune Suppression induced by Genetic, Therapeutic and Environmental Factors, had much the same message, which was also studiously ignored by the host of officials who attended. By 1998, adverse drug reactions had risen to the 4th leading cause of death in the United States and many people had begun, belatedly, to realize that much of drug therapy could be responsible for a literal epidemic of chronic degenerative diseases and organ dysfunction's which have occurred and are occurring during the 20th Century.

In Allopathic medicine, all diseases are classified as groups of signs and symptoms which usually have been recognized as a group or distinctive hallmark of a discrete illness. These are given names and from that point on, they are treated as an entity, known as the disease entity. In many of these, the cause of the disease is not known and treatment usually does not aim to remove or correct the cause or causes so much as to suppress the symptoms so the patient feels better.

Sometimes the causation of the disease is known or a cause is suspected and, in such cases, an effort is made to remove the cause. Many diseases are thought to be caused by bacteria and viruses; some of them are; in others, the bacteria appear after the tissue has been damaged by the disease and act as scavengers. Some diseases are caused by a lack of some one or more nutrients for which the body has a specific need and cannot make for itself. This lack leads to a breakdown in some essential process in the metabolism of a cell or group of cells which body stores of the nutrient are exhausted and not replaced by nutrition, either in the diet or by supplementation of the diet. Occasionally a disease might be caused by dietary excesses and intake of so much of a substance that the body cannot eliminate it or some metabolite of it – this happens, for instance, in gout. But whatever the mechanism, disease happens when the cells or some group of cells run out of energy and are no longer able to carry out their function or functions, and stay above the expression threshold of the inherited mitochondrial mutations.

Allopathic medicine has treated diseases by administering substances which have the effect

of masking symptoms, or attempting to do so. Increasingly, drugs which block some natural biological process were used to mask symptoms and were administered clinically for years to control symptoms of metabolic disorders, to lower blood sugar, to block hormone production, or to suppress enzyme production; these chronically administered drugs combined with chemicals in the food and water, as well as preservatives in milk, and meats also block life processes. Some of the processes blocked were in the mitochondria of cells, the organisms where energy is produced.

Mitochondria produce ATP in a complicated multi-step reaction, utilizing oxygen in its final step to combine with hydrogen, so that the waste product is water, a substance, which causes no damage to the structure of the cells. When this process is blocked or interrupted, energy production fails and free radicals are produced; these damage the structure. When cells are unable to produce energy they degenerate, become non-functional. They either become dormant or they become malignant and chronic degenerative disease is the result. If the process of energy production in the mitochondria can be restored, the cells and the organs they make can be restored to function – regenerated.

While many things are capable of interfering with mitochondrial function, pollution, extremely low frequency electromagnetic radiations, natural toxins, none does so more severely than chemicals, which are designed to interfere with biological function – pharmaceuticals, taken directly into the body at regular intervals for protracted periods of time.

The chemicals can be prescription drugs, over-the-counter drugs, street or illegal drugs, additives such as fluoride in the drinking water, aspartame used as an artificial sweetener or mercury leached from a tooth filling – whatever the source, chemicals capable of disrupting mitochondrial function will hasten the expression of degeneration in cells if regularly ingested.

The first step towards regeneration is to stop ingesting the chemical which is producing the degeneration. We must assume that most synthetic chemicals are capable of having, causing or contributing to this degeneration.

The next step is to detoxify the body to remove all such chemicals and residues of such chemicals from the body. This is accomplished by a number of steps including the use of nutrition.

Then the oxygen levels of the tissues must be enhanced and finally, the appropriate electromagnetic vibrations are applied. Some of these are known, but further experimentation

based upon our present knowledge of which of these have been successful needs to be done.

Chemicals capable of interfering with mitochondrial function are quite ubiquitous in the environment of everyone living in the late 20th century. They are in the food, the water, the air and the dust which accumulates on every surface of homes and work places. The task is to avoid as many of these as possible. Since most people cannot move to a pristine environment, if there are any more of these, the best that can be done is to make our environment as pure as possible.

We can filter and treat the air we breathe indoors. We can filter and purify the water we drink and bathe in. We can treat the foods we eat to remove most of the contamination and we can avoid eating foods that have chemicals added to them in the processing. We can shield our houses and offices from some of the harmful Electro-magnetic radiations; we can use appliances and devices which do not produce these and avoid those that do. We can stop consuming synthetic pharmaceuticals as drugs and find more natural ways to achieve relief from symptoms.

Regeneration of cells, tissues and organs, which have become degenerated, is an ongoing and arduous task. No one can do it for us – there is no magic solution. If we are to accomplish this, we must devote a considerable portion of our energy, time and income to it. The government cannot do it for us; in fact, quite a lot of our present exposure to these chemicals can be laid at the door of governmental agencies which are supposed to regulate our environment but fail to do so adequately.

The FDA and Department of Agriculture allow the inclusion in many foods of chemicals which produce degeneration. Many industrial activities produce some of the chemicals as a by-product of their operations and where the government is slack on regulation, these are allowed to be dumped in the air we breathe and the water we drink and bathe in.

We can begin by sharply questioning the premises of the Allopathic School and its knee jerk prescription of synthetic drugs for every minor ache or pain. People should quit gulping pills with serious effects for the treatment of minor aches and pains. We can re-explore the rich heritage of the use of herbs over the millennia, as well as Homeopathy.

People should quit buying milk which has been laced with formaldehyde and other chemicals so it can be transported for thousands of miles and stored for months. In the process, it has been devitalized, degraded and turned into a slow poison rather than a healthy food. We should

refuse to buy or eat meats, which have residues of antibiotics, hormones and other harmful chemicals, which can and do harm their bodies. It is possible to find natural substitutes for milk in the diets. Real milk is a wholesome food, but it is not really essential for adult diets.

The main point of ingress of chemicals which cause degeneration is through the digestive tract and the liver and a healthy gut can prevent a lot of assimilation of many chemicals. Unfortunately, due to years of ingestion of oral antibiotics, many people suffer from dysbiosis, an imbalance of the helpful bacteria, which live in the gut and their replacement by other organisms. If the ingress of some toxins is to be controlled, it is necessary to restore healthy gut foundation, replace the harmful bacteria with those which should be there, and restoration of normal function.

A good liver detox, under the supervision of a health care provider who understands this procedure, should be done. A course of EDTA chelation to remove heavy metal contaminants from the body and blood is probably essential for anyone over 40 years of age and should be done if they feel healthy, in order to stay that way. If they are suffering from one or more degenerative diseases, then a more comprehensive program is essential to regain health and maintain it.

Every patient suffering from a chronic degenerative disease involving mitochondrial function should have a comprehensive detox program, including saunas, hot baths, liver flushes, coffee enemas, ozone baths, Rolfing, Chiropractic adjustment, Acupuncture and Homeopathics, all as outlined in Krohn, et al, "Natural Detoxification".

In addition, a comprehensive program for nutritional supplementation adjusted to the individual and the diagnosis, should be implemented after examination by a physician.

As can be seen from a review of the rapidly growing literature on Mitochondrial Diseases, quite a few diseases which are due to mDNA deletions are manifest in infancy and early childhood, as syndromes, some of which are rapidly fatal, some of which can be treated. These distinct syndromes can be and should be treated in centers where this is diagnosed and treated. There is a growing awareness of much later onset of mitochondrial diseases which are due to decline in mitochondrial function with age due to mutations or to toxic influences with mitochondrial processes. Deficiencies in oxygenation and repeated episodes of ischemia and reperfusion which

lead to generation of Reactive Oxygen Species and other free radicals can lead to mitochondrial damage and decline in mitochondrial function.

To distinguish these from the infant and early childhood diseases, we call these acquired mitochondrial diseases and disorders. These acquired mitochondrial dysfunctions which lead to degeneration of tissues and organs can be treated, reversed and prevented by regenerative therapies, most of which can be carried out on an outpatient basis.

The relatively slow onset of some of these disorders, due to a gradual diminution of tissue oxygenation rather than the abrupt onset of ischemic disorders, leads to damaging of tissues rather than the apoptosis seen after ischemia and reflow. The affected cells become dormant; their metabolic fires banked and slowly smoldering rather than amply oxygenated, and such dormant cells can be brought back to normal or near normal function by appropriate measures.

Examples of such dormant cells are found in macular degeneration which can be reversed by electro-magnetic therapies; dormant cells in the penumbra surrounding infarcts in strokes which can be restored to function by hyperbaric oxygen therapy which avoids the excitotoxin induced apoptosis of reflow by supplying oxygen to the tissues, and the reversal of cardiac myopathy by pulsed electromagnetic therapy discussed below.

Since mitochondria are similar to bacteria, it should come as no surprise that antibiotics which attack bacteria, arrest their growth, can have a profound and oftentimes adverse effect on the structure and function of some of the mitochondria of the cells. Oral antibiotics, which affect not only mitochondria but gut flora adversely, creates a dysfunctional gut ecology which in its turn allows toxins to reach the cells of various systems and interfere with mitochondria ecology.

Mitochondrial DNA encodes for the production of a number of proteins which are essential

for the carrying out of oxidative phosphorylation. The production of these proteins is being studied by genetic biochemists who routinely utilize common antibiotics to block such protein processing. Some of the antibiotics so used are chloramphenicol, tetracycline, and erythromycin. Other chemicals are capable of acting as uncouplers of phosphorylation, i.e., sodium fluoride, which in many places is routinely added to the drinking water.

There is no way of knowing what synthetic compounds used either as drugs or as herbicides, pesticides and fertilizers or resulting from industrial processes, and capable of interfering with or interrupting the life processes of mitochondria, are routinely dumped into the aquifer from which they find their way into the human digestive system and eventually reach the mitochondria to disrupt mitochondrial function.

Antibiotics are singled out here along with fluoride as examples but there are thousands of synthetic compounds used therapeutically and industrially which are capable of affecting the structure and function of mitochondria, interfering with the production of energy (ATP) as well as causing the generation of Reactive Oxygen Species and other free radicals.

Thus, a person swallowing two capsules of an oral antibiotic along with a glass of typical urban tap water laced with fluoride, as "treatment" for a common cold, may well end up suffering serious consequences to his or her mitochondrial energy production and ultimately suffer tissue and organ degeneration as a result.

Many food additives used to extend the shelf life of processed foods may be capable of producing mitochondrial damage as well.

Meats frequently contain the residues of antibiotics which are included in the feed of. Some of these antibiotics remain in the meat whether beef, pork or poultry, along with hormones used for

promoting growth can reach the human digestive system, and where faulty bowel ecology exists may allow these to reach the blood and then be carried to organs and to the mitochondria of the cells of organs.

The healthy cell is in what Szent-Gyorgi termed the β or oxidative resting state, producing abundant energy for its work through oxidative phosphorylation, and the electron transport chain of the mitochondria; when something interferes with this oxidative function to decrease energy production significantly, the cell begins to revert towards the α state, its original primordial or anaerobic state. When it does so, it loses its functions and is barely able to maintain its structure - it has become degenerated. It may revert completely to the primordial state and resume the incessant mitosis characteristic of malignancy, or it may not reach that state and simply become dormant - living but not functioning.

Along this path to regression, there is always the possibility that it can be returned to the healthy oxidative state which sometimes occurs spontaneously. The cells have the capacity to return to normal function, but oftentimes this capacity is not utilized.

The purpose of treatment is to assist this return to normal function. The only treatments which offer hope of return to normal function are those which remove the causes of the regression and restore the capacity to return to function. These appear to be:

- (1) Detoxification
- (2) Orthomolecular nutrition
- (3) Oxidation
- (4) Pulsed electromagnetic stimulation at an appropriate frequency

These measures have been highly successful in restoring healthy function by restoring the

function of the mitochondria. Such treatments may be a bit more complex than appear from this short list.

Detoxification, the essential first step, is a multiphase process which involves nutrition. Fortunately, these have recently been described with great precision and in detail by Josephine Krohn, M.D. and her co-authors in their book "Natural Detoxification," Point Roberts, Washington, Hartley & Marks Publishers (1996) which constitutes a definitive manual of detoxification procedures.

This manual includes measures for the restoration of normal bowel ecology. This is important since the bowel is the ingress route for virtually all the toxins capable of interfering with mitochondrial function. Much nutritional therapy is involved in detoxing and to those processes the consideration that human mitochondrial DNA occurs in eight distinct haplotypes, which probably coincide to the eight metabolic types should be taken into account. Orthomolecular nutrition, in this case, means a basic diet which is appropriate for the individual's metabolic type. The cancer therapy of William Donald Kelly, one of the most consistently successful alternative cancer therapies developed to date, is based largely on this concept. There are certain nutrients which support oxidative phosphorylation and certainly these and the known antioxidants should be supplied along with the basic diet appropriate to the individual's metabolic type. Appropriate nutrition means not only the intake of nutrients which are correct but also the avoidance of the substances which can adversely effect mitochondrial function. The diet, both food and drink must, of course, not contain any of the mitochondrial toxins. The water must be free of any traces of fluoride as well as the hundreds of chemicals which are routinely found in certain water supplies. The foods must not contain traces of herbicides, pesticides, inorganic fertilizers, food colors or

additives, including those approved by the Department of Agriculture and the FDA for use as food additives or as within allowable limits for use as food. The tolerance for such substances in the treatment of mitochondrial dysfunction is zero. The foods and beverages must contain no aspartame or Nutrasweet - this product is currently found in over 5,000 commercial foods and beverages. It is reported to cause a mosaic, a number of conditions, particularly Multiple Sclerosis and Systemic Lupus, both of which are mitochondrial disorders. Reportedly, when this product reaches a temperature exceeding 86 degrees F. it converts to Formaldehyde and Formic Acid - below that temperature, it metabolizes to methylalcohol. There is more than ample evidence to absolutely exclude this product from the diet of anyone who is suspected of mitochondrial dysfunction. Some of the metabolic type diets include meats, and these must be free of antibiotic residues; seafoods should be confined to those originating and living well away from coastal waters, particularly seafood consisting of Northern fish caught at least 50 miles off shore. Poultry should be of the free-range variety and not that raised in crowded cages and fed antibiotics and other chemicals. Fruits and vegetables, to be eaten raw, should be thoroughly ozonated at the point of consumption to eliminate all herbicide and pesticide residues, and to destroy pathogenic bacteria such as E. coli 0157-H7, Salmonella and similar organisms involved in Food-borne Diseases¹. The toxins produced by such microorganisms can destroy mitochondrial function. Since toxins can be and are achieved transdermally, all bathing water should be purified by ozonation and not chlorination.

Another highly successful alternative cancer treatment, Essiac Tea, is an herbal

¹See Fox, Nichols, SPOILED: The Dangerous Truth About Food Gone Haywire, New York, Basic Books (1997)

detoxification. The tea must be brewed from absolutely pure water. Green tea is also reported to be an extremely efficient preventive of cancer and it too must be brewed from absolutely pure water.

Oxygenation: To the methods of oxygenation discussed in Krohn, et al's Natural Detoxification should be utilized. This is extra pulmonary oxygen enhancement by transdermal diffusion. In this method, the individual is immersed up to the neck in a tub of water through which Ozone has been and is being bubbled. This leads to a rapid rise in tissue oxygenation which, reportedly, lasts longer than the increased tissue oxygenation achieved with hyperbaric oxygen and eliminates the drawbacks inherent in HBO. It is far less expensive than chambers, it causes no difficulty with the ears, it does not cause claustrophobia and, since it is extrapulmonary, does not entail oxygen toxicity which is a pulmonary event. It can be engaged in as often as necessary to maintain high levels of oxygen in the extracellular fluid where it is readily available to the cells, and it avoids problems such as oxy-hemoglobin disassociation shifts.

So far only one pharmaceutical, Dichloroacetate, has been reported to be of any benefit in the treatment of mitochondrial diseases; all other pharmaceuticals should be suspected of being mitochondrial toxins. Some may not be, but until that is reliably established, they should empirically be handled as if they are. All synthetic compounds, those not occurring in nature, and synthesized from petroleum should be assumed to be capable of interfering with mitochondrial function.

Dental amalgam restorations are certainly capable of producing a mitochondrial toxin in the form of methylated mercury. Most other heavy metals should be avoided and where present in fat stores, should be removed by detoxification.

In the regenerative treatment of mitochondrial dysfunctions, if at all possible,

pharmaceutical treatments should be replaced by herbal, nutritional, homeopathic or other natural therapies. Sometimes this may not be possible.

During and after treatment, the principles of Natural Hygiene should be followed so far as this is possible in an urban environment.

Air and water can be filtered, oxygenated and sometimes electrostatically treated to remove pollutants.

Geopathic stress can be avoided. Bedding, such as mattresses and springs, can be replaced by air mattresses, which should be placed on wooden platforms to avoid all coil springs and other metallic support which can generate or accumulate electromagnetic frequencies. Some household appliances which generated high gauss magnetic fields can be eliminated. Quartz watches should not be worn on the body. Areas of Geopathic stress should be avoided, particularly for work and sleeping areas.

Acupuncture by a skilled practitioner can support many systems and organs energetically and can be a valuable aid for maintaining good bowel function, which is represented along several acupuncture meridians.

Spinal manipulation by a skilled Chiropractor or Osteopath can be crucial where the nerve supply to organs arises from the spinal nerve as well as the autonomic nervous system, the ganglia of which originate from the spinal nerves. Body work, Rolfing and massage therapies are also valuable in this sort of treatment - which is discussed in the book by Krohn, et al, as a part of detoxification procedures.

Psychological and spiritual counselling are of inestimable importance in all treatment programs.

All psychopharmaceutical drugs should be completely avoided in persons being treated for mitochondrial dysfunction, particularly the Selective Serotonin Re-uptake Inhibitors and diazepam derivatives, most of which can be replaced by herbal treatments. Drugs which alter brain chemistry almost certainly are mitochondrial toxins.

Blood pressure medications can and should be replaced by herbal and nutritional programs where possible.

Non-steroidal anti-inflammatory drugs are absolutely contraindicated in people suffering from mitochondrial dysfunctions.

Carbonated beverages should be avoided, those which are sweetened artificially with Aspartame as well as those which are unsweetened. All carbonated beverages are buffered with phosphate which severely interferes with normal metabolism.

Alcohol should be avoided. If this is not done, the intake should be strictly limited to one ounce of alcohol daily such as red wines. Stimulant beverages such as coffee and tea should be avoided, although green tea may be beneficial in moderation.

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