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A Paradigm Shift in the Treatment of Progressive Multiple Sclerosis

Hypoxia May Trigger Lesions: Oxygen and High-Dose Biotin Offer Promising Interventions

Multiple sclerosis (MS) strikes over 2.3 million people worldwide\(^1\), with about 200 new cases diagnosed each week in the U.S.\(^2\), and yet the disease is in many ways still a ‘black box’ of mystery. Why is the course so variable? What brew of genes and environment triggers the devastating symptoms? Is multiple sclerosis in essence a disease of inflammation, ongoing infection, or autoimmunity? Is it an amalgam of all three? Are there other etiologies?

An intriguing new framework is now emerging from European clinics and universities that offers a new answer: the lesions of multiple sclerosis may initially be triggered by a deficit of energy metabolism in neurons and their mitochondria (the energy powerhouses that populate every cell). In fact, mitochondria may play a key role throughout the different stages of the disease.\(^3\)

This is a new mechanism that has not been described before. Until now it was thought that white blood cells called lymphocytes attacked the body’s own tissue, directly leading to the inflammation, demyelination (stripping of the protective lipid sheath around a nerve cell), and neuronal (nerve cell) degeneration of MS.\(^4\) But though white blood cells and autoimmunity are key players later in the disease, it turns out that early demyelination can occur in the absence of lymphocytes.\(^5\) In its very acute, earliest phase, the lesions of MS may be triggered by hypoxia—insufficient oxygen—in neurons.\(^6,7\)

This new understanding zooms in on tissue energy metabolism, and fits beautifully with other recent, landmark research showing that high-dose biotin (a water soluble B vitamin known as vitamin B7) can stabilize and even reverse symptoms of progressive MS, possibly by restoring energy metabolism in atrophied neurons and myelin in atrophied neurons.\(^8,9\) As neuroimmunologist and physician Hans Lassmann, MD, of the Center for Brain Research at Austria’s Medical University of Vienna puts it: “Therapies which raise tissue energy levels over prolonged time periods may not only have a symptomatic effect, but may be neuroprotective.”\(^9\)

What initiating role does cellular energy play in early and ongoing disease?\(^10\) And what new therapies might emerge that maintain mitochondrial integrity and tissue metabolism?

A Curious Similarity Between Stroke and MS Lesions

In the early 2000’s, researchers began to probe striking concordances between early white matter lesions in stroke and similar lesions in multiple sclerosis. In a series of fascinating 2003 papers, Hans Lassmann noted that both stroke and MS share hypoxia-like metabolic tissue injury—a result of too little oxygen available to vulnerable neurons. When not enough oxygen is available, cells cannot function properly.\(^13,14,15\) It turns out that MS, as well as white-matter stroke and virus-induced encephalitis, are all marked by the presence hypoxia-inducible factor 1-alpha (HIF-1α),
a highly sensitive indicator of tissue injury due to hypoxia. HIF-1α most likely builds up as a response to changes within cells that, even if injured, have managed to survive the hypoxic conditions.12

For stroke, the damage and pathology are clearly vascular in origin. But for multiple sclerosis, Lassmann and others suggest that metabolic disturbances alone might initiate the injury. The damage could be triggered by excessive excitotoxins (such as the amino acid glutamate, which functions as a neurotransmitter in the brain). Excitotoxins might damage and interfere with functioning of the mitochondria. Mitochondria are the energy powerhouses of every cell, and when they suffer from collapse or dysfunction, the entire cell is compromised. Glutamate and other excitatory neurotransmitters are indeed increased in multiple sclerosis16,17,18 and can injure the brain’s highly sensitive neuronal network. “Such a mechanism may in part be responsible for tissue damage in a demyelinating brain,” write Lassmann and colleagues. Metabolic injury due to hypoxia might lead to demyelination of the axon—the long thread-like part of a nerve cell, along which impulses are conducted.4

In highly active lesions, free radical damage is present in the form of reactive oxygen species (ROS) and reactive nitric oxide intermediates (RNI), which may also directly impair mitochondrial function, metabolism and cellular energy. The resulting tissue damage leads to a metabolic hypoxia that looks like the hypoxia in stroke.3 Oxygen tension in the central nervous system is normally relatively low anyway. Within the white matter of the brain, however, it is especially low—and MS lesions often show up there.10 Cells called oligodendrocytes are particularly vulnerable to hypoxia, because they have the demanding task of creating the myelin sheath around axons (a single oligodendrocyte can support the myelin of 50 axons) and supporting axon function with molecules necessary for energy metabolism.19 In addition, mitochondrial dysfunction occurs in chronically demyelin-ated axons, leading to hypoxia-like tissue injury.20 Mitochondria are central to axonal degeneration in all stages of MS, and play a significant role in energy metabolism and cell homeostasis.3

**Tissue hypoxia may play a key role in two of the most important aspects of MS: neurological deficits and demyelination.**

...was preserved around axons in the animals treated with oxygen. “Understanding how the experimental lesion is formed,” the researchers write, “has revealed a novel therapeutic strategy to prevent the demyelination from occurring...tissue hypoxia [may] play a key role in two of the most important aspects of MS, namely the production of neurological deficits, and at least some of the demyelination.” The scientists go on to speculate that...
High Dose Biotin: Another Novel Approach to Restoring Tissue Metabolism

"No drug to date has been found to have any impact on progressive multiple sclerosis," says neurologist and neuroscientist Frédéric Sedel, MD, PhD, of Salpêtrière Hospital in Paris, France.22 But what about a vitamin? Sedel’s surprising research demonstrates that high doses of the water soluble B vitamin biotin (also known as vitamin B7) may be able to stabilize or even reverse progressive MS, preventing its relentless decline.23

Biotin is highly bioavailable, and both absorption and excretion are rapid. At doses up to 20 milligrams in humans, excretion of biotin and its metabolites are similar for intravenous dosing and oral supplementation, indicating 100% bioavailability of oral biotin.24 The vitamin is mainly eliminated through the urine.25 Biotin has many functions in the body—such as regulating blood sugar and helping the body metabolize fats and proteins26—but where MS patients are concerned, it may offer two other benefits.

One, it increases levels of adenosine triphosphate (ATP) via the mitochondria, which supplies every cell with energy. Two, it promotes myelin repair by helping the body synthesize fatty acids.8 It does this by acting as a coenzyme, or helper, for a molecule called acetylCoA carboxylase. Thus, maintains Sedel, it could potentially alleviate MS symptoms in two ways. First, by increasing ATP levels and reversing the functional or so-called “virtual hypoxia” found in MS. Secondly, it may promote direct myelin repair.

In the initial pilot study conducted by Sedel and colleagues, 23 patients aged 23 to 76 years, with primary and secondary progressive MS, were treated with high doses of biotin (100-300mg/day) from 2 to 36 months, for an average of 9.2 months. All patients had disease that was progressing for a minimum of the previous twelve months. Patients were evaluated by various methods—four patients who had visual loss from chronic optic neuropathy were given vision tests; in 18 patients who had spinal cord involvement, walking distance and muscle strength were tested. Clinical exams were videotaped, and typical MS symptoms such as fatigue, swallowing difficulties and urinary dysfunction, were measured. Videotapes of nine patients, both before and after treatment, were viewed and rated ‘blindly’ (not labeled as to whether the video was taken before or after treatment) by an independent, specialist center.27

Biotin Leads to Quantitative and Qualitative Improvement

Results of treatment were impressive. The four patients with optic neuropathy had improvement in visual acuity after 3 months of treatment. Sixteen of the 18 patients with spinal cord involvement displayed improvement after 2-8 months on the biotin. Seven patients who had paraparesis (partial paralysis of the lower limbs) improved. The supplement was well tolerated with virtually no adverse effects, except diarrhea in two patients. Overall, 21 of 23 patients experienced qualitative and quantitative improvement. The dose of 300 mg/day was associated with the best overall clinical response. “The results were in marked contrast with the natural history of progressive forms of MS where almost no spontaneous or sustained improvement occurs,” writes Sedel. 25

At the April, 2015 American Academy of Neurology (AAN) conference in Washington, DC, results of a randomized Phase III trial with both placebo and control groups were presented.28 After twelve months of treatment, patients on biotin had overall, global improvement that was significant. Walking scores were improved compared to the placebo, and a statistically significant number of patients showed confirmed improvement at nine and twelve months compared to the best scores obtained at two visits before treatment. Not one patient in the placebo group improved to that level. The relapse rate was 3.9% in the biotin group and 7.8% in the placebo group (not statistically significant).

At the April, 2016 AAN conference in Vancouver, 24 months of results were presented. High dose biotin significantly reversed disease pro-
progression compared to placebo for the first 12 months of the study, and the benefit was sustained over the second 12 months. Lead study author and neurologist Ayman Tourbah said at the presentation: "This is the first time that a 'drug' has reversed the progression of the disease in a statistically significant proportion of patients. In addition, if we look at the mean Expanded Disability Scale (EDSS) change, the data compare very favourably with all previous trials that looked at the same endpoint. Almost no progression was observed in patients treated with...[high dose biotin] for 24 months and this has never been observed before. When we compare these results to other trials in progressive MS that involved more than 6,000 patients overall, this is clearly the best effect size ever observed. Results...point to the fact that targeting neuron and oligodendrocyte metabolism represents a promising and novel disease modifying approach in progressive MS." 

Are We Missing A Deeper Mechanism in Tissue Energetics?

Pediatric gastroenterologist Donald Mock, MD, PhD, of the University of Arkansas, believes this research points to a fundamental mechanism by which biotin might help tissue energetics. Mock has a doctorate in biochemistry and a long standing interest in water-soluble vitamins and health. He has written peer reviewed papers about biotin and was an author on a 2015 paper with Sedel that discussed high dose biotin, hypoxia and MS.

"It looks as if there may be neurologic conditions where there is impairment in energy transduction, in ATP production, in myelin synthesis, all of which may respond to biotin," says Mock. “There is something profound that these findings are trying to tell us,” he continues. "I think if we pay enough attention, we may discover that nerve specific energetics are impacted by biotin." Mock says, for instance, that he is fascinated by a different study on biotin-responsive genetic basal ganglia disease. The basal ganglia area of the brain is affected in diseases such as Parkinson’s and Huntington’s. In hereditary basal ganglia disease, symptoms can be severe and disabling, including marked confusion, difficulty swallowing, paralysis and coma. Early treatment can halt the disorder. Ten patients in Saudi Arabia responded well to a combination of high dose biotin along with thiamine. The researchers suggest renaming the disease: “biotin-thiamine responsive basal ganglia disease associated with SLC19A3 gene mutations.” Overall, says Mock, “both this and the MS study suggest we take a closer look at these B vitamins and their effect on tissue hypoxia and energy metabolism.”

Mock and other researchers note that although the supplement is well tolerated, further safety studies need to be carried out. In addition, five patients in the biotin group had apparent hypothyroidism, but it was due to high plasma biotin levels interfering with testing assays, producing misleading results. This could apply to other tests that involve similar assays which utilize (strept)avidin-biotin technology. It

**Recommendations for Tests Using (strept)avidin-biotin Technology**

Various laboratory tests, including tests for thyroid function as well as cardiac, fertility, hormonal, bone metabolism and more, may rely on (strept)avidin-biotin technology, and raised levels of biotin in the blood may possibly interfere with results. Here are important points to know.

- In five reported cases, high doses of biotin likely affected results of thyroid function laboratory tests that used (strept)avidin-biotin technology.
- The amount of biotin that may interfere is variable across tests. Some have an interference threshold at about 100 ng/mL of plasma biotin (meaning that below 100 ng/mL the results are not biased, and above 100 ng/mL results are biased), while the threshold can be as low as 5 ng/mL for other tests.
- Instruction manuals for some of the interfered tests indicated that, “In patients receiving therapy with high biotin doses (>5 mg/day), no sample should be taken until at least 8 hours after the last biotin administration.”
- In the studies for progressive MS, biotin is given at 100 mg three times daily. Preliminary research indicates that after a washout period of between 5-15 days, a biotin plasma level < 5 ng/mL is achieved, and the test can be safely taken. Research is ongoing.

**References**

2 Personal communication with Delphine Bernard, PhD, Project Leader, R&D, Medday Pharmaceuticals, Paris, France, on June 9, 2016
is suspected that a washout period of between 5-15 days would be necessary before utilizing tests based on this technology.24 Sedel emphasizes that biotin seems to help only in progressive MS patients, not in those who are in a relapsing-remitting phase: “Biotin doesn’t help accelerate recovery after relapse, it only helps when you are progressive.”21 He believes the vitamin works on the consequences of demyelination, and that it may also help genetic diseases of the myelin, such as Adrenoleukodystrophy (a disease that became famous in the movie Lorenzo’s oil) and Charcot-Marie-Tooth disease.

Reframing multiple sclerosis—and perhaps other neurological conditions—as diseases that in part are due to hypoxia, impaired mitochondrial function, and faulty tissue energetics, opens a new way forward to novel treatments. In a 2009 paper, researchers at Oregon Health and Science University in Portland suggested that: “evidence is evolving that mitochondria are key players in axonal degeneration in all stages of MS, playing crucial roles in energy metabolism and cell homeostasis. Anti-inflammatory agents do not completely prevent axonal injury and are largely ineffective in treating progressive MS...therapies that target mitochondria and enhance their functional warrant investigation.”7

References:
1. http://www.nationalmssociety.org/What-is-MS/MS-FAQs
10. http://www.nationalmssociety.org/What-is-MS/Types-of-MS
28. http://www.neurology.org/content/86/16_Supplement/S49.004.short
29. http://www.neurology.org/content/84/14_Supplement/S49.004.short
32. Personal conversation, May 24, 2016

Focus: You are a neurologist who specializes in inborn errors of metabolism (IEM)—genetic diseases that develop due to disorders of metabolism. Can you tell us how and why you became interested in that unique aspect of neurology?

FS: The majority of IEM are due to defects of single genes. Mutations can result in functional defects that result in disease later in childhood or adulthood, presenting mostly with neurologic and psychiatric symptoms.1 It is a very special field that most neurologists are not familiar with, yet IEM can be responsible for a lot of clinical diseases, and many of these patients can be helped. In my general practice, of one thousand patients suffering from totally inexplicable neurologic diseases, we were able to find IEM in about 15% cases. They may be amenable to treatment by changes in diet that reduce the buildup of toxic compounds, supplements of a missing enzyme, stimulation of the residual enzymatic activity, or of alternative pathways through cofactors or substrates, or simply through medication. I was fortunate to study with the world expert

Have We Discovered a New Class of Biotin-Responsive Neurological Conditions?
An Interview with Neuroscientist Frédéric Sedel, MD, PhD

Focus August 2016
on IEM, Jean-Marie Saudubray. He is lead author on hundreds of widely cited papers and the classic textbook in the field, “Inborn Metabolic Diseases: Diagnosis and Treatment,” which is now in its fifth edition. He was initially trained in neonatology and saw very sick newborns and children. Because of his work we now have hundreds of regimens that work well in neonates. It is always most effective to treat early in the disease course, but even for older children and adults, even if irreversible damage has occurred, treatment can still be partially effective.

**Focus:** In many instances, you will never know what the genetic error is. So how do you treat anyway?

**FS:** Dr. Saudubray and I worked to classify IEM into five distinct groups. For each group we listed the kind of clinical signs that might be related to these kinds of inborn errors, and the kinds of treatments that might be effective. In daily practice that is very practical, because once you are able to classify the IEM, you are able to try some of the likely interventions, even if you don’t know the genetic error that has caused the disease. It is a very rational way to link biochemistry to clinical practice. You can find these classifications in our paper, but for instance, errors of metabolism might include fatty-acid β-oxidation defects, and disorders involving key cofactors such as thiamine, biotin, riboflavin, vitamin E and coenzyme Q10; while errors of intoxication might include porphyrias, urea-cycle defects, homocystinurias, and more.3

**Focus:** What was one of your most amazing successes?

**FS:** I will never forget a woman with severe schizophrenia. She was very impaired and had been for at least a decade. Then one day she developed a paraplegia with no explanation. That brought her into our clinic. The paraplegia was mysterious and unique and we found this patient had a very specific enzyme defect, in the gene that makes methylenetetrahydrofolate reductase (MTHFR). It was not a polymorphism, it was a true and severe mutation, and we treated with cofactors such as betaine, folic-acid, and vitamin B12, and within a few months the patient completely recovered from her schizophrenia. She was just like you and me.

**Focus:** That’s impressive. Now tell us how your work on IEM led you to the extraordinary discovery of biotin-responsive progressive MS.

**FS:** That’s a long, surprising story. First, I should clarify that MS is not due to an IEM, but it is a metabolic disorder. For the axon to function correctly, myelin must be intact. Without intact myelin, you get a kind of acquired metabolic disease that in the case of progressive MS, appears to respond to high-dose biotin. In our case, we were treating optic nerve atrophy. We knew that patients with optic nerve disease always have a metabolic defect. Every genetic disease that codes for optic nerve atrophy is linked to defects in energy metabolism for nerve. Once you know that you can try different co-enzymes that affect that pathway. One of those is biotin. It has some unique properties that are very important for energy metabolism in the axon, and for helping generate myelin. This was where we were very lucky. We treated five patients with optic nerve atrophy who did respond to high-dose biotin. But we thought we had discovered a new genetic disease!

**Focus:** How did you discover you were wrong, and that you had stumbled onto a treatment for progressive MS, as it turns out?

**FS:** We undertook genomic sequencing on those five patients, and we did find a mutation in a

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**Biography:** Frédéric Sedel, MD, PhD, is co-founder and Chief Executive Officer (CEO) of MedDay Pharmaceuticals. He is a trained neurologist and neuroscientist who studied Inborn Errors of Metabolism (IEM) with the legendary Jean-Marie Saudubray at the Necker Children’s Hospital in Paris. In 2004, Dr. Sedel founded and coordinated the Neurometabolic Department of Pitié-Salpêtrière Hospital, dedicated to treating adults with IEM. Dr. Sedel has been part of the Reference Centre for Lysosome Diseases, Vice President of the French Society for IEM, and President of the SSIEM European Adult Metabolic Group. He has published 80 peer-reviewed articles, mostly dedicated to IEMs in adult neurology, and has spoken at more than 30 leading international conferences over the last 5 years.
Thyroid Under Threat

Could Iodine Deficiency Be More Widespread Than We Think?

Back in the third millennium BCE, our ancestors relied on iodine-rich seaweeds and sea sponges to treat goiter, a painfully enlarged thyroid gland caused by iodine deficiency. They did not know why the sea was a source of healing. It was not until the 1800’s that the trace element iodine was actually discovered; a purple vapor wafting out of seaweed ash that had been treated with sulphuric acid in order to produce gunpowder. Named iodine—after the Greek word ioeides, or violet-colored—this potent and essential trace mineral was soon found to be present in high levels in the thyroid gland.

We now know that iodine is essential for synthesis of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Thyroid hormones regulate protein synthesis and enzymatic activity, and are critical for the body’s normal metabolism. An iodine deficiency, therefore, can lead to slowed metabolism, weight gain, hypothyroidism, fatigue and intolerance of cold, as well as neurological, gastrointestinal, and other symptoms. Thyroid hormones are nec-

gene for the chloride channel, but only in two patients. The other three had no genetic error we could find. So we were obviously wrong. We did realize, however, that one of our patients had progressive MS. So we decided to investigate high dose biotin in other progressive MS patients, and this is what we published initially. We treated 23 patients and the effect was absolutely amazing. The rest is, as they say, history. (See FOCUS, pp. 2-6).

We have much more data this year. At the April meeting of the Academy of American Neurologists, we disclosed the full data from two further, classically controlled studies. One was in those with progressive MS, both primary and secondary, and the other in those with progressive or relapsing-remitting MS who were suffering from optic neuropathy. We very clearly observed an improvement in optic neuropathy in patients with progressive MS, not in those with non-progressive, relapsing-remitting MS. This tells us that biotin does not help accelerate recovery after relapse. It only helps once you are progressive. I think this makes sense. By that time you have axonal degeneration. Biotin has no effect on inflammation, but it probably has a very profound effect on axonal metabolism, and that must be the major route through which biotin works in progressive MS.

Biotin has no effect on inflammation, but it probably has a very profound effect on axonal metabolism, and that must be the major route through which biotin works in progressive MS.

Focus: Why don’t normal doses of biotin work? And how did you arrive at 300 mg as the ideal dose?

FS: What is a normal dose? It’s presumably in the food you eat. But one way to activate a defective pathway is to use very high dose of co-enzymes. Three hundred milligrams a day turned out to be the dose which had the best efficacy. When we decreased the dose to 100 mg daily the effect was decreased, or completely vanished. And when we increased the dose to 600 mg a day it was not well tolerated by patients. They experienced anxiety and tremor, so the dose was clearly too high. That’s very empirical, but 300 mg a day works nicely. In addition, our studies indicate that 300 mg is already near the plateau of maximum absorption. It is probably both the highest dose that can be absorbed and also well tolerated.

Focus: Are there other demyelinating diseases for which high dose biotin might be effective?

FS: We hope so. We are conducting a trial in x-linked muscular dystrophy, which is a disease of the myelin made famous in the film Lorenzo’s Oil. We are also trying it in genetic peripheral neuropathies such as Charcot-Marie-Tooth disease.

References:
2 http://www.amazon.com/Inborn-Metabolic-Diseases-Diagnosis-Treatment/dp/3642434207
5 Marie-Tooth disease. We are also trying it in genetic peripheral neuropathies such as Charcot-Marie-Tooth disease.
necessary for normal skeletal and central nervous system development and may play a role in immune response as well as help prevent or reverse fibrocystic breast disease.

Supposedly iodine deficiency is a problem of the past. In the early 20th century, many people living in the “goiter belt” (the Great Lakes, Appalachians and Northwestern regions of the United States) suffered from significant iodine deficiency. Up to 70% of children in these areas had goiter. In the U.S., iodized salt first became available on grocery shelves in Michigan in 1924. Today, iodized salt graces nearly every restaurant table and the kitchens and dining rooms of most homes—its regular use supposedly eliminating goiter. In addition, iodine is abundant in sea vegetables, seaweeds, as well as scallops, shrimp, yogurt, sardines, salmon, eggs and other foods.

And yet, it seems many of us may not be getting adequate iodine. The emphasis on low-salt diets, or on natural ‘sea’ salts, has decreased the national consumption of iodized salt. In addition, neither the US nor the UK requires iodized salt in processed and fast food products. A New Zealand study found that adults were mildly deficient in iodine, and adding iodized salt to bread improved levels, as indicated by a 24 hour urine iodine concentration test. A 2016 editorial in the Lancet notes that, “We’ve known since 2011 that the UK population is mildly iodine deficient. In fact, the country now ranks seventh among the ten most iodine-deficient nations in the World… Findings from some studies have shown that low maternal iodine concentrations during pregnancy are associated with reduced verbal intelligence quotient (IQ) and reading abilities in children.”

Lack of iodine can lead to thyroid nodules. Incidence of thyroid nodules in the U.S. is surprisingly high. In a study of over 5,000 individuals over age 60 in Framingham, MA, clinically apparent thyroid nodules were present in 6.4% of women and 1.5% of men. Yet this may underestimate incidence. In autopsy studies, up to 50% of patients had thyroid nodules and using ultrasonography, around three-quarters of women had at least one thyroid nodule. Autopsies also show evidence of chronic autoimmune thyroiditis in 27% of adult women, with a rise in frequency over 50 years, and 7% of adult men, and diffuse changes in 5% of women and 1% of men. These disturbing trends should make all of us ask - what’s going on with our thyroid?

**Thyroid Under Siege**

Iodine is a member of a chemical family called halides—a group of five nonmetallic elements. These are fluorine, chlorine, bromine, iodine, and astatine. Because they are missing an electron from their outermost shell, they react easily with most metals to form salts. The one we all know best is sodium chloride—or table salt.

One possible source of our thyroid troubles is the omnipresent burden of synthetic toxic halogens in our environment—especially those that are fluorine, or bromine-based—that can compete with and displace iodine. We are exposed to synthetic and potentially harmful halides daily. Synthetic perfluorinated compounds—the perfluoroalkyl acids (PFAAs)—are used in everything from stain and water resistant coatings for carpets and furnishings to fast-food contact materials (such as wrappings), fire-resistant foams, paints, and hydraulic fluids. A 2010 study of nearly 4,000 healthy adults found that those with high blood levels of perfluorooctanoic acid (PFOA), and a related molecule substance called perfluorooctane sulfonate (PFOS) were twice as likely to have thyroid problems as those with the lowest levels.

Brominated flame retardants also harm the thyroid; polybrominated diphenyl ethers (PBDEs) disrupt circulating levels of thyroid hormones (THs), potentially affecting growth and development. These flame retardants are used as additives, and migrate easily from their source products into the indoor and outdoor environment. Postmenopausal women, according to a 2016 study, may be at particular risk. Women with lipid-adjusted serum concentrations of BDEs in the highest quartile of exposure had higher odds of having a current thyroid problem compared to women with lower serum concentrations. These associations were much stronger in an analysis that was restricted to postmenopausal women.

Fluoride present in our water, toothpaste and some dental fillings may also compete with iodine and potentially disturb thyroid function. In addition, we may be exposed to bromine through that universal

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sustenance: our daily bread. It has been legal since 1914 to use an additive called potassium bromate when baking bread in the USA. Potassium bromate bleaches and enhances the elasticity of dough. The end product is fluffy, soft and white. It is a known carcinogen, and is not allowed as a food additive in the United Kingdom, Canada, Brazil and the European Union.

According to a report by the Environmental Working Group (EWG), “in tests on lab animals, exposure to potassium bromate increased the incidence of both benign and malignant tumors in the thyroid and peritoneum – the membrane that lines the abdominal cavity. Later research confirmed and expanded these findings, concluding that ingesting potassium bromate resulted in significant increases in cancer of the animals’ kidneys, thyroid and other organs.” The EWG lists at least 86 environmental contaminants and a related molecule substance called perfluoroctane sulfonate (PFOS) were twice as likely to have thyroid problems as those with the lowest levels.

How to Measure Iodine Levels

Iodine levels can be measured in the urinary iodine concentration (UIC), after urine has been collected for 24 hours. Mild deficiency is a UIC of 50–99 μg/L; moderate is a UIC of 20–49 μg/L and severe is a UIC of less than 20 μg/L. Other tests can refine the diagnosis: Thyroglobulin (Tg) is the building block for thyroid hormones, and requires iodine to function. Blood Tg levels are elevated with iodine deficiency.

A 2010 study of nearly 4,000 healthy adults found that those with high blood levels of perfluorooctanoic acid (PFOA), and a related molecule substance called perfluorocane sulfonate (PFOS) were twice as likely to have thyroid problems as those with the lowest levels.

References:


2. Chatin A. Recherches sur l'iode des eaux douces; de la presence de l'iode dans les eaux du monde; du sautéed veggies, anyone?


11. http://my.clevelandclinic.org/health/diseases_conditions/brcThyroid_Nodules


Focus: You state in your book that our ongoing exposure to increased amounts of toxic halogens—bromide, fluoride, and chlorine derivatives—necessitates that we ensure that our iodine levels are optimal. Can you tell us how your attention first turned to iodine deficiency?

DB: For the first ten years of my practice I found I was diagnosing a lot of people with thyroid problems. I live in Michigan, which is known as a goiter-belt, because the soils are deficient in iodine. My usual response was to put my patients on thyroid hormone, but I wondered why so many of them needed it in order to feel well. I went back and looked at the cofactors needed to make thyroid hormone, and I had my patients supplement with those cofactors, such as selenium, B vitamins, and magnesium, but nothing worked as well as thyroid hormone. During that time I tried iodine as well, and though I didn’t see any bad effects, I did not see much good, either. I was frustrated. And there was not a great test for iodine deficiency during those first ten years. Then I read a letter Guy Abraham, MD, wrote to the Townsend newsletter. In it he explained a new iodine loading test he had developed. I called him and our phone conversation soon led to in-person meetings. He was interested in my practice because I was in the middle of a goiter belt.

We started testing my patients using his iodine loading test. Today, I’ve tested a little over 7,000 individuals. According to this test, over 96% of them are deficient in iodine, with most being severely deficient. (The World Health Organization classifies Iodine deficiency as mild, moderate, or severe.)

Focus: What is the iodine loading test?

DB: You take 50 mg of iodine as a loading dose, as a pill or an oral solution, depending on where you source it. You then collect urine for the next 24 hours. You check to see how much was excreted during that time period. Since most oral iodine is excreted through the urine, you can measure the amount taken versus the amount excreted. The more deficient an individual is, the more he or she will hold on to the iodine. Our collated research has shown that approximately 90% excretion of a loading dose of 50 mg is normal.

Focus: Has this test been independently corroborated?

DB: No, not officially, and there has been some criticism of the test for that reason. But from my standpoint, I’ve also taken spot urine tests for iodine, which are widely used. You simply pee in a cup and the iodine level is checked. There are reference ranges for that. Most of my patients also show up markedly below the reference range on spot tests, corroborating the iodine loading test.

Focus: What form of iodine supplementation do you use?

DB: For the first ten years of my practice I was using potassium iodide only, and as I mentioned, the effects were negligible. I was one of those people on thyroid hormone. When I checked my iodine levels they came up low on both a spot test and a 24-hour loading test. After meeting with Dr. Abraham and conducting research with him, we realized a combination of iodine and potassium iodide were better. Different tissues of the body preferentially take up different forms of iodine. For example, the breast preferentially absorbs iodine, while the thyroid likes iodide. To get a whole body effect it’s better to take a combination of iodine and iodide. I myself have been able to lower my dose of thyroid hormone by half after supplementing with both forms of iodine.

Focus: Are you able to test for the toxic halogens as well?

DB: I can test for bromine. We have toxic ranges for that chemical, and there is no known therapeutic value anyway, so theoretically your levels should be close to zero. Our environmental exposure to
bromide is so pervasive, I feel that if you stop taking iodine you will accumulate bromine. It’s in everything from computers to clothing to food. Fluoride is in everything from tap water and pools, to fertilizers, to drugs, to toothpaste. But I don’t know how to accurately test for it, since it binds tightly to the bones, and you’d have to do bone biopsies. I have presently tested over 1,000 patients for their bromine levels, and nearly 100% tested high.

**Focus:** What is the average dose most patients take?

**DB:** Average doses of iodine vary from 12.5 to 50 milligrams. Most of my patients are on about 25 milligrams. If they have thyroid, endocrine, or breast disease, they may need a little more iodine in order to normalize their iodine related cell architecture.

**Focus:** What do you say to respected colleagues who feel these high doses are questionable and potentially harmful?

**DB:** I have three physicians and a nurse practitioner on my staff in a busy, full-time practice. We’ve been doing this for over twelve years now. Either our patients are different than what these other doctors are talking about, or we’re right. I can see side effects with iodine but they’re very rare. Often they are due to iodine displacing fluoride and bromide from the tissue, and usually easily managed by adjusting the dose or adding more salt.

As for precipitating a thyroid disorder, yes, it can happen, but in my practice it is uncommon. I’ve only seen 3 cases of hyperthyroidism in twelve years. In addition, some researchers and endocrinologists believe that excess iodine intake can lead to autoimmune thyroid problems. But there are numerous reports in the scientific literature, some dating back well over 100 years, showing the benefits of using iodine in excess of the RDA to treat autoimmune thyroid illnesses.

I do see detoxification reactions in about 5% of patients. The use of iodine results in the release of the toxic halides from the body. If the body’s detoxification pathways are overloaded when the toxic halides are being released, a detoxification reaction can be triggered, taking the form of fatigue, muscle aches, fever, diarrhea and brain fog. It can be minimized by using a comprehensive holistic treatment program with nutritional support, healthy foods, and other helpful, natural treatments. I also suggest adequate use of unrefined salt and supplementation with magnesium and vitamin C helps.

**Focus:** You are often asked why so many of us would need to take so much iodine.

**DB:** Yes, that’s the most common question I am asked by both physicians and laypeople. The short answer is, because the majority of people are iodine deficient. Our food supply is deficient in iodine, partly because we are all eating less iodized salt. If a lowered iodine intake was the only problem, it would be simple to rectify iodine deficien-

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### Caveats for Supplementing With Iodine Beyond the RDA

Iodine supplementation should be carried out under a doctor’s supervision. Inappropriate iodine supplementation can sometimes lead to hypothyroidism, apparently due to a protective mechanism by which the body decreases formation of thyroid hormone production when subjected to high doses of iodine. This has been observed in susceptible individuals after high doses of iodine for medical diagnostics, and in newborns with exposure to povidone iodine cleaning solutions. The acute effect usually lasts about two days, but in some individuals the hypothyroid state may persist and require thyroid replacement hormones. Sometimes, iodine restriction alone is enough to return thyroid levels to normal.

Occasionally, high dose iodine can lead to hyperthyroidism or thyrotoxicosis. At worst, this condition can lead to heart failure. A study of over 1000 individuals in Brazil after 5 years of excessive iodine supplementation due to high table salt iodine found urinary iodine levels elevated in over 45 percent of those studied. Chronic autoimmune thyroiditis was present in 16.9%, affecting women nearly twice as much as men. In addition, a characteristic, itchy rash suffered by some individuals with celiac disease, and known as dermatitis herpetiformis (DH), can flare up with iodine exposure. According to John J. Zone, MD, Professor and Dermatology Chair at the University of Utah and Celiac Disease Foundation Medical Advisory Board member, “There is little question that ingestion of large amounts of iodine dramatically worsens DH. It should be understood that iodine does not cause DH. It worsens DH. Gluten causes DH.”

### References

cy. However, as I’ve said, our exposure to toxic halides are occurring at levels that humans have never experienced. We eat brominated bakery products. We are exposed to brominated flame retardants. Our water supply is fluoridated. Many pesticides and insecticides for lawn care contain toxic halides.

In my opinion, there is no single nutrient that has a more positive effect on more people than iodine. To me, it’s a foundational element of a healthy life, like eating a healthy diet and exercising. Every cell in the body needs and requires iodine for optimal function and to maintain a normal cell architecture. If you look around, too many people have thyroid nodules, thyroid cancer, and autoimmune thyroid disease. I feel the common denominator is iodine deficiency, probably due to competitive inhibition by all the toxic halogens in our environment and food.

References:

Acetylation: Key to Enhanced Absorption
A Fresh Look at Two Potent Precursors to Glutathione

Like a boat setting sail for an exotic port or a basketball arcing through the air on its way to the hoop, nutrients must end up at their intended destination to make a difference. Until a nutrient has been absorbed and utilized by the cell that needs it, it really hasn’t nourished us. It is all potential, but not yet action.

The absorption and utilization of nutrients depends on many factors, but at the final gateway of the cell, a nutrient crosses the cell membrane either through passive diffusion across the membrane, or active transport with the assistance of other molecules. Acetylation— which simply means adding a functional acetyl group (with the chemical formula CH₃CO) to a compound—allows certain nutrients to be better utilized.

When acetylated, both cysteine and glutathione function as potent precursors to reduced (unoxidized form) glutathione. Low glutathione levels have been widely documented in aging and neurodegenerative disorders, as well as cystic fibrosis and viral infections. According to Marty Jones, PharmD, and Michael Ash, DO, ND, “Strategies to boost reduced glutathione levels are of marked therapeutic significance. Its protective effects extend to eyes, skin, kidneys, lungs, intestines, and the immune system.” Glutathione deficiency contributes to oxidative stress, which plays a key role in aging and the pathogenesis of many diseases (including kwashiorkor, seizure, Alzheimer’s disease, Parkinson’s disease, liver disease, cystic fibrosis, sickle cell anemia, HIV, AIDS, cancer, heart attack, stroke, and diabetes).

N-Acetylcysteine and S-Acetyl Glutathione: Potent Antioxidants
Glutathione has often been called the mother of all antioxidants. It is a water-soluble tripeptide molecule and one of the most important, primary detoxifying metabolites we have. Our body makes it, and replenishes it when its stores are depleted. It is the most abundant intracellular antioxidant in animals, plays important roles in antioxidant defense, nutrient metabolism, and regulation of cellular events (including gene expression, DNA and protein synthesis, cell proliferation and apoptosis, signal transduction, cytokine production and immune response, and protein glutathionylation). Within the cell, glutathione is kept in its reduced (unoxidized) form, and maintaining adequate levels of reduced glutathione is critical to survival. This has never been more true than today, when we are living in a sea of pesticides, industrial chemicals, persistent organic pollutants, including toxic halogenated compounds, as well as pharmaceutical overuse and abuse (see FOCUS, Making The Case for High Dose Iodine, Page 11).

As important as glutathione is, evidence for a direct effect of oral glutathione on plasma and cellular levels of glutathione is mixed. Some studies suggest that, over
a period of months, a diet high in glutathione or boosted by glutathione supplements, can indeed raise levels of glutathione in humans.\textsuperscript{9,10} Other studies show that, at least in the short term, plasma levels do not increase, perhaps in part because regular glutathione is broken down into its components, cysteine, glutamate and glycine, and the body must then recombine them to make new glutathione. In one double-blind, randomized, placebo-controlled 2011 study of 40 healthy adult volunteers, the researchers noted that, “There were no differences in oxidative stress biomarkers between treatment groups before the study began. Then one group of volunteers were given 500 mg of oral GSH supplement twice daily for 4 weeks, another group received placebo. At the end of the study total reduced glutathione (GSH), oxidized glutathione (GSSG), and the ratio of GSH to GSSG (indicator of oxidative stress) were unchanged in both groups compared to the results obtained before supplementation. It was concluded that no significant changes were observed in biomarkers of oxidative stress, including glutathione status, in this clinical trial of oral glutathione supplementation in healthy adults.”\textsuperscript{11}

Those individuals seeking optimal exposure to the benefits of glutathione may turn to two, acetylated, oral nutrients. N-acetylcysteine (NAC), the first, is a potent precursor to glutathione, and well known for its ability to treat acetaminophen overdose through its liver-protecting properties; as well as loosening thick mucus in cystic fibrosis or chronic obstructive pulmonary disease.\textsuperscript{12} NAC is a modified form of the amino acid cysteine—altered by adding an acetyl group to its N-terminus. It has been safely used as a supplement for years.\textsuperscript{13} Pharmaceutical grade NAC is so effective that it’s on the World Health Organization’s list of essential medicines.\textsuperscript{14}

NAC is rapidly absorbed after an oral dose, but is metabolized in the small intestine and liver into metabolites that work in the body in many beneficial ways.\textsuperscript{15} First, it reduces cystine (removes oxygen that has oxidized cysteine) and transforms it back into cysteine, which can be transported into the cell 10 times faster than cystine. Second, since cysteine is the rate-limiting precursor of glutathione formation, NAC serves an indirect facilitator of GSH and detoxification. NAC can increase intracellular GSH levels in red blood cells, liver cells, and lung cells.\textsuperscript{16} In fact, the weight of evidence suggests that NAC is most effective in cases where glutathione is depleted. In vitro research shows that NAC increases levels of glutathione within platelets and decreases reactive oxygen species. Its strength is the replenishment of GSH in deficient cells.\textsuperscript{17} Plasma levels of glutathione peak within six hours of an oral dose of NAC.\textsuperscript{18} Third, NAC is a scavenger of hypochlorous acid (HOCl), a potent free radical produced by our white blood cells to help them fight infection and control response to injury.\textsuperscript{19} NAC can also lower levels of both homocysteine and lipoprotein(a), which when elevated have been linked to atherosclerotic disease.\textsuperscript{20,21,22} Furthermore, hyperhomocysteinemia has been associated with neurodegenerative disorders.\textsuperscript{23}

NAC can lower inflammatory cytokines such as TNFα, IL-6 and IL-1β.\textsuperscript{24,25} In animal research, it has been shown to reduce acute kidney and liver injury due to pesticides.\textsuperscript{26,27} Its free-radical scavenging activity and its ability to replenish glutathione may be helpful in alleviating glutathione may be helpful in alleviating glutathione, and improving insulin sensitivity in type-2 diabetes, according to researchers at El Manar University in Tunisia. The researchers reviewed one hundred papers demonstrating the antioxidant, anti-inflammatory and anti-apoptotic properties of NAC. They note that these properties, along with the fact that NAC can modulate signaling pathways in insulin target cells and pancreatic β cells, render it a potential therapeutic molecule in the treatment of type-2 diabetes.\textsuperscript{28}

Overall, NAC’s profoundly protective effects are attributed to both its antioxidant and anti-inflammatory actions.\textsuperscript{29} NAC also has strong evidence for its efficacious use in psychiatric disorders.\textsuperscript{30}

**S-Acetyl-Glutathione:**

**Stable Precursor to Reduced Glutathione**

Along with NAC, an oral acetylated form of glutathione called S-Acetyl-Glutathione (SAG) has been demonstrated to boost glutathione levels in humans. SAG is a stable molecule, a variant of reduced glutathione that has an acetyl group added in to its S-terminus. SAG remains intact in the gut and is de-
the total doses in this pilot study were equal, seven daily doses and one weekly dose are not necessarily physiologically equivalent, and thus this study is only suggestive.)

According to chemist Andrea Zacagnini, PhD, cofounder with chemist Mauro Staderini, PhD, of Arké Organics, an Italian company that synthesizes organic compounds, “Acetylation facilitates absorption of glutathione through the intestinal wall. But once it is in the bloodstream, its half-life is about fifteen minutes. It is possible that during that fifteen minutes some is absorbed into cells, but after that fifteen minutes, it reverts to the simple form of reduced glutathione. However, that is very effective. The reduced glutathione is then available for all the biological functions that require it. And it’s certainly easier than IV administration. And remember, reduced glutathione is not simply an antioxidant. It is one of the main tools that our body uses for detoxification and removal of heavy metals.” Zacagnini says she has been particularly impressed with reports from patients with Chronic Fatigue Syndrome (CSF, also known as Myalgic Encephalitis, or ME). “With a bit of care in the dosing, I’ve heard of patients who have radically changed their life for the better with this product.”

Overall, both NAC and SAG offer useful and simple ways to increase levels of our master antioxidant, glutathione.

References:

2. Laval OS, Adhowale KO. Effect of acetylation and succinylation on solubility profile, water absorption capacity, oil absorption capacity and emulsifying properties of mucuna bean (Mucuna pruriens) protein concentrate. Naturun. 2004 Apr;49(2):128-36. PMID: 1514970

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