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Orthomolecular medicine is defined as the therapeutic use of substances that occur naturally in the body. Originally defined in the context of treating and preventing psychiatric diseases, the intent of orthomolecular therapy is to provide the optimal molecular environment for the brain and other tissues by altering the intake of nutrients such as vitamins (and their metabolites), minerals, trace elements, macronutrients, as well as other naturally occurring metabolically active substances.

Mission Statement

The mission of the Journal of Orthomolecular Medicine is to advance knowledge and improve the practice of orthomolecular medicine by educating practitioners of orthomolecular medicine, inspiring scholars, students and future leaders with novel, relevant and high quality metabolic research, clinical studies and reports, informative topic reviews and well-argued commentaries. The Journal aims to engage the orthomolecular medicine community by providing a forum for debate and the promulgation of new ideas.
Toxicology of Vitamins*

Vitamin supplements can cause adverse reactions (ADRs) when prescribed properly. No therapeutic intervention, whether it is a medication or vitamin supplement, is without risk. Even my favourite vitamin (i.e., niacin) was implicated in causing five major effects (not deaths) in 2010 and seven major effects (not deaths) in 2009 from data collected by the American Association of Poison Control Centers. When an event is denoted as causing a “major effect,” it means that: “The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).”

Despite the reality that vitamin supplements can be implicated in serious ADRs, the overall advantages to taking vitamin supplements involve their low incidence of side effects, their extremely low risk of causing fatalities, their cost and affordability, their relative ease of use, and their therapeutic effectiveness. The most important point to emphasize is the extremely low risk of fatalities associated with vitamin supplements. The American Association of Poison Control Centers has been collecting data on the fatalities associated with numerous products (i.e., vitamin supplements, medications, household cleaning products, etc) for decades. There have only been 12 deaths linked to vitamins from 1983 to 2010.

Medications, on the other hand, have a less than stellar safety record. In a meta-analysis of hospitalized patients, 106,000 patients had fatal ADRs, making medications between the fourth and sixth leading cause of death in the United States in 1994. Another report estimates that deaths due to ADRs from medications to be about 100,000 annually in the United States. If we estimate the annual death rate due to medications in the United States from 1983-2010, then some 2,700,000 deaths can be attributed to medications compared to only 12 from vitamins during the same time period.

Another method that we can use to compare the toxicities of medications to vitamin supplements is by calculating their respective therapeutic indexes (TIs). The TI represents an estimate of medication safety, for a very safe medication would be expected to have a very large toxic dose in comparison to a smaller effective dose. It is calculated by determining the ratio of the LD50 (i.e., the dose required to produce a lethal effect in 50% of the population) to the ED50 (i.e., the median effective dose at which 50% of the population exhibits a specified therapeutic effect). Of course, the actual TIs of medications and vitamins are not calculated with exact precision, but are extrapolated from experimental studies, animal studies, drug trials, and accumulated clinical experience. It can be inferred that the TIs of medications are much narrower than that of vitamins as a result of being more toxic. In other words, the amount of medication that produces a lethal effect would be closer to the amount needed to produce a therapeutic effect.

To further illustrate this concept, let us compare the TI of diazepam to that of vitamin B6 (pyridoxine). Both agents are used to treat similar neuropsychiatric disorders, such as anxiety and seizures. In an experimental study in mice, the TI of diazepam was calculated to be 350 (LD50/ED50 = 49 mg per kg/0.14 mg per kg). I have calculated the TI of vitamin B6 by using LD50 data from a material data sheet and ED50 data from a published study. Thus, the TI for vitamin B6 in mice is 12,791 (LD50/ED50 = 5500 mg per kg/0.43 mg per kg); a result that is much greater than that of diazepam, suggesting that the risk of toxicity would be much less even when very large (“mega”)...
doses are prescribed. The point here is not to disparage medications, as we are all fully aware of their essential therapeutic properties. My point, rather, is to simply state that vitamin supplements are much safer due to their apparently wider TIs and their tremendous safety record.

Jonathan E. Prousky, ND, MSc.
Editor

References
The treatment of diabetes in 2012 is among the least successful in medicine, despite billions of dollars spent on research and the many scientists whose careers are focused on diabetes. Medicine has succeeded in making diabetes a very expensive disease for the patient while at the same time making it a cash cow for the numerous businesses that primarily cater to the diabetic. We would expect to have achieved at least some improvement in the treatment of diabetes; in fact the basic protocols haven’t changed much in twenty years. Is research getting close to a solution? In my opinion as a pharmacist, the answer is no.

Diabetes has become a managed disease, although I think the word “managed” is exaggerated, for “managed” would mean the patient is regularly going to the doctor while being in good health because of the doctor’s treatment.

For fifteen years I was the pharmacy manager for a small neighbourhood family-owned business. My position allowed an unusual observation point, where I saw the results of several people over a long term as they were introduced to the “sugar-med treadmill.” It was not evident to me that these people improved from their diabetes treatment. All of the severe diabetics seemed to have the same group of symptoms: they were overweight (you never lose an ounce after the doctor introduces you to hyperinsulinaemia), oedematous, suffered from poor exercise tolerance and had a generally unhealthy appearance. The number of people with peripheral neuropathy was notable. I would periodically ask people how they were doing. At the time, I wasn’t as suspicious as I am now, since I have also been diagnosed with a fairly serious case of type II myself. I wasn’t greatly surprised about developing diabetes as it runs in my family (my mother and sister both have the diagnoses), but when I developed severe foot neuropathy symptoms, I started doing my own research.

Due to my job, I was already aware of the poor treatments for the foot neuropathy. Ami-triptiline, gabapentin, and lyrica don’t have much effect. People usually are introduced to heavy narcotics before they get any real relief. The drugs dull the pain but there is no real healing going on because medicine claims they don’t know the source of the pain in the first place.

Medicine still considers the HgbA1c as the “holy grail” of treatment outcome for diabetes. I asked people about their HgbA1c values; it was interesting to note how many of these extraordinarily unhealthy looking people had HgbA1c values in the normal range. Consequently their doctors wouldn’t change their diabetes treatment (regardless of their health complaints) because these people were normal from a blood test reference point.

With medicine’s dogged pursuit of the HgbA1c values in mind, I decided to examine closely the whole presentation. The most frequent argument is that diabetes is a disposal issue. The sugars in the blood have a geography problem. The body seems interested in urinating the sugars (and calories coincidentally) away, whereas what the body would be doing if there wasn’t something supposedly wrong would be making the cell membranes be more permeable and allowing the sugars to be burned intracellularly.

Medical research is spending virtually all of their time and money making the membranes more permeable. I call this ‘barrier breech’ research. The body is deliberately closing the gate to excess calories and medicine is trying to re-open it. If you think about what happens when those extra calories flood into the cell and are metabolized what do you get? Do you get advanced glycated end products (AGEs) that the body views as a threat and decides to do something about?

In the middle of this speculative argument comes a UK researcher named Paul Thornalley, who wrote a paper in 2005 detailing the diabetic symptoms that form when there is an acute thiamine deficiency.1 How do diabetics develop thiamine deficiency? When a diabetic’s sugars start to rise they start losing thiamine at a rate 16-25 times higher than normal. Somewhere in the distal tubule area of the kidney there is a failure to re-uptake thiamine which it normally does (this loss is so high that it is, arguably, impossible to
correct through diet alone). As the thiamine loss becomes body wide and acute, all of the symptoms of type II diabetes appear. Polyneuropathy, nephropathy (of the kidneys), retinopathy (of the eyes) and heart failure (in particular, left ventricle ejection fraction)—are all symptoms of acute thiamine deficiency. So do you have diabetes or do you have acute beriberi?

I was diagnosed with type II diabetes three years ago and immediately balked at the diabetic med treadmill. My doctor wanted to place me on statins, metformin and Byetta, which I refused to take. The Life Extension Foundation (LEF) suggestion for the fat-soluble thiamine called Benfotiamine was approximately 250 mg four times a day. I also added the vitamin B₆ metabolite, pyridoxal 5’ phosphate. This vitamin was listed in a LEF article as protecting the kidneys from AGEs. The dose for me is 100 mg/day. I also add in magnesium aspartate, pyridoxine and acetyl l-carnitine, depending on the severity of neuropathy of my feet. My doctor was in disagreement with my choice but I told her I was doing it this way until I was convinced it wasn’t working.

I started the vitamin regimen and did minimal monitoring of my condition for 2.5 years. I was watching for the supposedly inevitable deterioration of my health due to my elevated blood sugars. Ignoring your elevated blood sugars is at your peril, according to the doctors. You will have kidney issues, your pancreas will stop cooperating and your vision will become blurry as your sugars cause retina damage. When I started this experiment my fasting blood sugars were typically between 160-190 when I woke up in the morning and my HgbA1c was about 8.9. The only sign of some active problem was the neuropathy of my feet. I had all of the symptoms of diabetic neuropathy: numbness of my toe area, shooting pains in my joints. I also had the feeling that the general circulation in my feet was poor as my feet were always cold.

As the months went by my doctor (who was aware of my experiment and a little sceptical) kept asking me when I was going to get sick. Jokingly, I said maybe I’m not going to. So now after approximately 2.5 years since my last blood tests I got my results. I was actually afraid to look at the results and finding that I had finally outsmarted myself and got hurt. There is quite a propaganda machine built around the treatment of diabetes. As I drove over to retrieve my blood tests I did a mental check-up of how I felt. I ended up thinking that I can’t have a lot wrong with me, I just plain feel too good. Vision, weight (I’ve lost 35 lbs), energy levels and psychological attitude were all fine. All of these parameters are supposed to have gone haywire by now…correct?

Well, my blood test results are almost like science fiction and I hope you’ll agree. After letting my blood sugars run rampant for 2.5 years I have no discernible health defects that can be related to my still elevated blood sugars.

Treating my diabetes symptoms was not complicated because I got some early positive feedback. The neuropathy of my feet was the symptom that I wanted to solve. The pain in my feet was so great that it was interfering with my job as a pharmacist, as I am standing a lot. I didn’t even want to try the treatments (mostly revolving around different types of painkillers) to solve my foot problems. My first inkling that there were other ideas came from a pamphlet from a Florida doctor who thought that there was a great deal of correlation between diabetes and beriberi. The logic path is as follows. As a diabetic’s sugar levels raise, the kidneys for some reason start sloughing off thiamine (failure to re-uptake) 16-25 times higher than normal. At a loss rate like this, replenishing body stores through diet alone is probably impossible. Supplementation will be necessary.

As I started absorbing the new thiamine information the association between mainstream medicine’s treatment of diabetes and thiamine manipulation was hard to visualize. Diabetes treatment by manipulating the blood sugar levels (using HgBA1c as a guideline) seems sensible but at the same time the results aren’t encouraging. Millions of people currently have diabetes and millions more are diagnosed every year. I know it’s not a very scientific observation but people with diabetes don’t look very healthy. They tend to be oedematous and overweight. The longer the people are on the sugar-med treadmill the
worse these symptoms seem to become.

Within a short time the most overt of the neuropathy symptoms started to subside. The shooting pains with the “ice-pick in the ankle joint” symptoms were mostly gone in seven days. All of the other symptoms of numbness of the toes and overall pain of the feet including the ‘boot effect’ the (feeling that you have your boots or socks on) are mostly gone in three weeks. Now this isn’t a cure…it is a control. The symptoms are held at bay as long as you keep your thiamine levels high. If you quit taking benfotiamine, the symptoms come roaring back. Some other vitamins are involved in keeping the foot pain at bay including 200mg/day of B6, and alpha-lipoic acid (600 mg/day).

Mainstream medicine tells you to keep your HgbA1c values low or your health suffers. My HgbA1c values have been elevated at and my fasting blood sugar levels around 190. Values like these are supposed to guarantee a poor quality of life, from a health standpoint. These values have been in this approximate range for 2.5 years so my poor health should have evidence in my recent blood tests:

- HgbA1c 9.1% Scale = 0.0-5.7 (high)
- Glucose, fasting 190 mg/dL Scale=65-99 (high)
- BUN 17mg/dL Scale = 7-25 (normal)
- Creatine 0.82 mg/dL Scale = 0.76-1.46 (low normal)
- Albumin 4.2g/dL Scale 3.6-5.1 (normal)
- Bilirubin 0.4mg/dL Scale = 0.2-1.2 (low normal)
- ALK 85 IU/L Scale = 40-115 (normal)
- AST 31 Scale = 10-35 (high normal)
- ALT 37 Scale = 9-60 (normal)
- eGFR 95. Scale = > 59
- Cholesterol 178mg/dL Scale = 125-200 (normal)
- Triglycerides 174mg/dL Scale = 0-150 (high)
- SED Rate 5mm/h Scale 0-20 (low normal)
- Creatinine, urine 86.7mg/dL Scale 20-370 (low normal)
- Microalbumin/Creatinine ratio 9.2mg/GCr Scale 0-30

The creatinine and microalbuminuria values are the so called “Canary in the Coal mine” values. The kidneys are supposed to go first when AGEs have started your march to health failure because you didn’t keep your HgbA1c values within range.

I think 2.5 years is long enough for this concept to fester. I have also had my eyes checked for sugar based destruction of my retinas. I have no retinopathy caused by hypercholesterolemia, blood pressure and more importantly no sugar/retina issues of any kind. I am 61 years old and have 20/25 vision in both eyes.

Where is the predicted failure of my health due to hyperglycemia? I have two underlying values. Is it possible the values are unimportant in predicting overall health? It is important to remember that these results did not come from doing nothing. What I did do was substitute several nutritional substances for pharmaceuticals. A question could be, instead of the body destruction from diabetes being an active process from AGEs are the health issues actually nutritional shortages that can be augmented?

I am hoping this simple (and non-toxic) experiment on me will open up some serious discussions about diabetes. Having diabetes is complicated (and expensive). Once someone shows you which ones to take, taking vitamins is relatively simple. It’s also cheaper than the other method. I am spending $100-150 per month on nutritional supplements. During this 2.5 year experiment I have not given my doctor a single dime for advice on how to regulate my HgbA1c value.

If nothing else I’m hoping my home experiment will generate some spirited discussions about the validity of substituting vitamins in diabetes treatment. But this editorial is also an attempt to unseat some basic tenets of the medical fiasco known as diabetes. The prevalence in 2011 of type 2 diabetes worldwide according to the World Health Organization (WHO) is 346 million, and some 3.4 million people died in 2004 as a consequence of the disease. The WHO predicts that the deaths attributable to diabetes will double between 2005 and 2030. With this kind of projection a “Manhattan Project” kind of response seems necessary.

So what is the intellectual problem that seems so intractable to the medical research community? The medical community seems ignorant of the projections for prevalence as virtually all levels of medical treatment from
family practice to endocrinologists use the same stale protocols as the diabetes prevalence goes up every year. The obvious lack of improvement in most people’s health from being placed on the “sugar-med treadmill” doesn’t seem to register on their physicians. The people are oedematous, lethargic, have poor exercise tolerance and are constantly gaining weight. I’m not sure these symptoms qualify as health improvements.

The observation failures by the physician were exposed by the ACCORD trial failures.\(^3\) The ACCORD trials were meant to validate once and for all that the closer a patient got to the almost magical HgA1c value of six the healthier a person became. Instead, there was a 22% increase in mortality from heart failure. This unexpected value caused the FDA to terminate the trial midstream. Is it possible that the HgbA1c value is not a relevant value in evaluating diabetes as an illness?

The HgbA1c value can obviously be moved up and down with some predictability. The catch is exposed by the ACCORD trials. One would think the value is showing a direct relationship between this value and health. But what if there is no correlation? What other values would you use to show diabetes’ effect on the body?

If you go to PubMed and together use the keywords “thiamine deficiency” and “diabetes” you will get over 120 references. Why this isn’t a mainstream argument for therapy is truly sinister. I wouldn’t mind seeing some narrow minded endocrinologists (with whom I have butted heads with recently) into getting reprogrammed. Supplement-based nutrition therapy is utterly neglected in conventional management of diabetes.

Diabetes is big business. The National Diabetes Fact Sheet reported that in 2007, the direct medical costs of diabetes nationally was estimated at $116 billion (USD).\(^4\)

While feeling overwhelmed by a diagnosis of hyperglycemia, patients often are comforted by the complicated explanations and the sudden increase in activity and attention. The possibility that they are being misled just doesn’t come up. Even if patients decide to do their own research it’s confusing. The cause of diabetes is basically unknown but with some major alterations to one’s lifestyle and lots of chemicals liberally applied will allow the patient to lead a relatively normal life. For the truly curious, a large, relatively comprehensive, block of information can be discovered.

The internet has a great deal of alternative information, of which doctors are mostly ignorant. If the patient were to present this information, the doctor would likely comfort the patient while telling him that they are getting the cutting edge treatment and all the patient has to do is keep a close watch on their HgbA1c value. As long as that number is idolized, everything will be okay. Even after three years of looking at the results of the ACCORD trials, there has been no major correction of treatment protocols for type II diabetes that addresses the unexpected mortality issue.

If this argument is even partially correct, the implications for mainstream medicine are staggering. These ideas need discussion in front of the right people. People with diabetes need some new ideas.

–Stuart Lindsey, PharmD

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References
Schedule Dependence in Cancer Therapy: Intravenous Vitamin C and the Systemic Saturation Hypothesis

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Abstract  Despite the significant number of in vitro and in vivo studies to assess vitamin C effects on cancer following the application of large doses and its extensive use by alternative medicine practitioners in the USA; the precise schedule for successful cancer therapy is still unknown. Based on interpretation of the available data, we postulate that the relationship between Vitamin C doses and plasma concentration x time, the capability of tissue stores upon distribution, and the saturable mechanism of urinary excretion are all important determinants to understand the physiology of high intravenous vitamin C dose administration and its effect on cancer. Practitioners should pay more attention to the cumulative vitamin C effect instead of the vitamin C concentrations to account for observed discrepancy in antitumor response. We suggest that multiple, intermittent, short-term intravenous infusions of vitamin C over a longer time period will correlate with greater antitumor effects than do single continuous IV doses of the same total exposure. This approach would be expected to minimize saturation of renal reabsorption, providing a continuous “dynamic flow” of vitamin C in the body for optimal systemic exposure and clinical outcomes. This prevents the “systemic saturation” phenomena, which may recycle vitamin C and render it less effective as an anticancer agent. Nonetheless, more pharmacokinetic and pharmacodynamic studies are needed to fully understand this schedule-dependence phenomenon.

Introduction  The pharmacokinetics and pharmacodynamics of intravenous (IV) vitamin C (Ascorbic Acid, Ascorbate, AA) has been partially described by various groups.1-7 Nevertheless, the issues of schedule dependence and dosage in relation to cancer therapy have not been thoroughly discussed.

The use of large doses of AA has been utilized for the treatment of cancer by various groups.8-10 The inhibitory action on cancer cells by AA has been described since 1952.11 High concentrations of AA may induce apoptotic cell death in tumour cell lines, possibly via its pro-oxidant action.12 Moreover, high doses of AA in the presence of oxygen favour the formation of hydrogen peroxide, providing an additional mechanism of anticarcinogenic action.12 Another anticarcinogenic action induce by high doses of AA is angiogenesis inhibition.13 Our group has also observed that higher concentrations of AA increase adenosine triphosphate production probably by increasing mitochon-
drial electron flux. In contrast to this, lower concentrations of AA display antioxidant properties that may prevent the activation of oxidant-induced apoptosis and prevent the formation of hydrogen peroxide. These concentration dependent behaviours of AA may in part explain the seemingly contradictory results reported previously on AA effects on cancer.

**Discussion**

**IV Vitamin C**

The concentrations of AA toxic to cancer cells in vitro can be achieved clinically by intravenous administration. Currently, IV AA is used extensively by alternative medicine practitioners in the USA (11,233 patients treated in 2006 and 8,876 patients in 2008). Clinical studies evaluating AA in cancer outcome have been done. As much as a 70-fold difference in plasma concentrations is expected between oral and IV administration, depending on dose. As a matter of fact, the pharmacokinetics of orally administered vitamin C has been early postulated to be dose-dependent, as the fraction absorbed decreased with increasing dose due probably to a saturable intestinal pump-mediated absorption mechanism.

In addition, the systemic clearance of vitamin C seems to be increased with accumulative exposure, a process that has been well-described by Hickey et al in the so-called “Dynamic-Flow Model.” Briefly, under physiological conditions, vitamin C is normally removed through glomerular filtration by kidneys, but a fraction of this filtered amount is returned into the body by capacity-limited tubular reabsorption. Thus, this concentration-dependent tubular reabsorption of vitamin C by the kidneys is saturated at supra-physiological levels of ascorbate and, therefore, a shorter terminal vitamin C elimination half-life is observed in individuals who receive excessively high amounts of vitamin C by continuous IV infusion. We think an IV schedule affording very high doses (>100 g) or continuous infusions will overload the body stores for vitamin C, as well as block its dynamic flow processes. In this context, it is necessary to take control of the dosing schedule for vitamin C delivery into the body so that the required systemic levels are obtained (i.e., those necessary to have in vivo anticarcinogenic activity, but not too high that can saturate the non-linear recycling process in kidneys and hence increasing the vitamin C clearance).

We have hypothesized that giving vitamin C intravenously by following a fractioned schedule over a longer period (i.e., by multiple-days, intermittent short-term IV infusions of high doses instead of using the conventional long-term continuous IV infusion administration) will provide the optimal levels for anticarcinogenic activity. Such a schedule is expected to minimize the saturation of renal vitamin C reabsorption while providing a continuous “dynamic flow” of AA in the body for optimal systemic exposure and effect.

We firmly believe that a good understanding of all these mechanisms and their further implementation in clinical practice will yield better therapeutic outcomes. Accordingly, a concentration-function approach to vitamin C provides new insights into its physiology and pharmacology. With IV administration, ascorbate is turned from vitamin to drug, as pharmacologic concentrations are produced that are as much as 100-fold greater than maximal oral dosing.

In some circumstances continuous infusion of IV vitamin C does not seem to be the optimal therapeutic schedule for cancer and repeated administration over a longer time period should be favored. We believe this particular pharmacokinetic-pharmacodynamic behaviour of high dose IV vitamin C can be explained by the Systemic Saturation hypothesis.

**Systemic Saturation Concept in Relation to IV Vitamin C**

Systemic saturation results when the concentration of AA in plasma and tissues in the body are high enough to produce an adverse effect in the biochemical parameters or metabolism. In this way, AA’s conversion to
Dehydroascorbate (DHA) is reversed back to AA. Once this takes place, the prooxidant action is decreased, thus AA anticarcinogenic and/or carcinostatic action is reduced. This physiological phenomenon may occur when high IV doses of AA (100g or more) are given in a continuous schedule. When high doses of IV AA are given continuously, it overwhelms the cellular biochemical pathways favouring the reversion of DHA to AA. This particular action dismisses AA anticarcinogenic and/or carcinostatic activity. This concept may in part explain the contradictory results reported previously in clinical studies despite in–vitro evidence that high concentrations kill cancer cells. The continuous high dose AA may pose a physiological stress to the body that may cancel or overcome the same physiological mechanisms we are trying to modify.

A pilot pharmacokinetic study of vitamin C at high dose infusions in a cancer patient suggested a dual–phase kinetic behaviour of ascorbate in vitro. This disposition pattern depends on the actual infusion–generated plasma ascorbate concentrations with respect to the saturation cut–off level (ca. 70 µM = 0.123 mg/dL). All these parameters are relevant to understand the physiology of high dose IV AA.

Conclusion

While AA alone may not be enough of an intervention in the treatment of most active cancers, it seems to improve quality of life and extend survival time. It should be considered as part of the treatment protocol for all cancer patients.

Despite multiple in vitro and in vivo studies using different schedules of vitamin C for cancer therapy, the exact administration schedule that maximizes antitumour response remains unknown. Researchers should pay more attention to the cumulative (net) vitamin C effect instead of the vitamin C concentrations. Again, we speculate that the schedule–dependence in the pharmacokinetics of AA accounts for such a discrepancy. The relationship between AA dose, steady–state plasma concentration, tissue store or cell compartments concentration/distribution, and urinary excretion is important to understand its physiological effect or more related to this discussion, its effect on cancer. In this regard, we suggest that prolonged schedules of intravenous vitamin C would yield greater antitumour effects than would single continuous IV doses of the same total exposure. As such, administration schedules reaching effective antitumour concentrations are more likely to result from intermittent IV infusion delivered on multiple–days. Nonetheless, more pharmacokinetic and pharmacodynamic studies are needed to fully understand this phenomenon.

Competing Interests

The authors declare that they have no competing interests.

References


Metabolic Correction: A Functional Explanation of Orthomolecular Medicine

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Abstract Vitamins, minerals and other micronutrients take critical roles in a wide variety of highly complex and integrated cellular processes in human biochemistry. The rate and extent of the enzymatic activity that determines these processes depend on the bioavailability of these micronutrients. The healthy state where optimal (maximum) functioning, health and wellbeing is achieved; may be attained by metabolic optimization. This state is achieved when we facilitate the metabolism to reach full velocity and completion of reactions which can be considered the optimal metabolic equilibrium. A combination of genetic makeup, diet, trauma, diseases, toxins and environmental stressors among others are conditions that will often elevate the demand of nutrients in order to achieve the optimal metabolic equilibrium. Metabolic Correction is a functional biochemical/physiological concept that explains how improvements in cellular biochemistry help the body achieve metabolic or physiological optimization. Brilliant minds such as Roger J. Williams, Linus C. Pauling, Jeffrey Bland and Bruce N. Ames have contributed in a fundamental way to our understanding of the importance of micronutrients to attain the healthy state. The Metabolic Correction concept becomes important since our food is decreasing in nutritional value; diseases increase the demand for nutrients and medications can deplete nutrients. These nutrient insufficiencies are causing enormous cost due to increased morbidity and mortality. In summary, Metabolic Correction increases enzymatic function that enhances biological functions contributing to better health and wellbeing.

Origin of the Problem
Maximum or optimal health requires metabolic harmony. The multiplicity of critical functions of vitamins, minerals and other nutrients at the cellular level, and especially their role as cofactors in enzyme reactions that protect genes from mutations and repair gene damage is probably unrecognized or unappreciated by most health professionals. It can be argued that the true importance of vitamins in human biochemistry is far from fully elucidated, simply due to the high complexity of cellular processes. What is commonly ignored and not fully appreciated is the essential role that various minerals play in human biochemistry. Critical enzymes require such metals as copper, zinc, manganese, selenium, etc. as an integral part of their molecular structure or mechanism of action. Enzymes play a critical role in regulating and orchestrating the rates of the multitude of biochemical reactions that take place in living organisms.

Metabolic nutrition is generally recognized as the study of how diet and nutrition affect the body’s metabolism. Nutrition
in general is a very complex science but its importance is relatively easy to understand. Aside from starvation there are three levels of nutrition: poor, fair, and good. Poor nutrition brings severe underdevelopment to the young as well as deficiency diseases such as beriberi, scurvy, pellagra, rickets, kwashiorkor and all the ill defined combinations and variations of these afflictions. Fair nutrition is good enough to prevent the well-defined deficiencies, but not good enough to promote good health and proper development. This mediocre nutrition is unfortunately the kind which we have been taught to regard as satisfactory. Good nutrition is the one that provides not only the needed energy but high quality protein, carbohydrates and fats; in addition to the necessary vitamins and minerals. The concept of a balanced diet was developed to prevent deficiency diseases based on the knowledge that an appropriate mixture of food items will provide the minimum requirements of the nutrients needed by the body. We should be aware that this supposedly good nutrition may not be enough for physiological optimization leading to excellent health. We should acknowledge that food alone may not provide sufficient micronutrients for preventing deficiency.

Inadequate dietary intakes of vitamins and minerals are widespread, most likely due to excessive consumption of calorie-rich, nutrient poor, refined food. Sub-optimal intake of micronutrients often accompanies caloric excess. These inadequate intakes may result in metabolic disruptions. Episodic shortages of micronutrients were common during evolution. Natural selection favours short term (emergency) survival at the expense of long term health. Short term survival was achieved by allocating scarce micronutrients by triage. As micronutrients become scarce, a triage mechanism for allocating scarce micronutrients is activated. This triage means prioritization of the use of relatively scarce nutrients to the most fundamental life preserving functions. In metabolic reactions, enzymes involved in adenosine triphosphate (ATP) synthesis would be favoured over deoxyribonucleic acid (DNA) repair enzymes; as well as the production of immune system components and neurological chemicals. When there is a lack of synergistic components of the metabolic network, an array of negative metabolic repercussions arise, eventually leading to loss of healthy physiological equilibrium and the acceleration of degenerative diseases.

Metabolic Correction

The Metabolic Correction concept provides the biochemical elucidation of the utilization of nutrients for preventive and therapeutic purposes against disease. Metabolic Correction is a functional biochemical/physiological concept that explains how improvements in cellular biochemistry help the body achieve metabolic or physiological optimization. Impaired or incomplete cellular biochemical reactions are remedied with Metabolic Correction.

The History of Metabolic Correction

Brilliant and incredibly knowledgeable pioneers provided the groundbreaking basis of what we call Metabolic Correction. Their innovative scientific contributions have substantially advanced our understanding of molecular nutritional biochemistry, and especially how it can influence the pathological or disease state.

In 1947, Dr. Roger J. Williams, contributed to the evolution of the molecular origin of disease with the development of the concept of “Biochemical Individuality,” which refers to the differing nutritional needs for optimal function among different people. He also described anatomical and physiological variations among people, and how these impacted their disease susceptibility and nutritional requirements.

“Molecular Medicine” was a term used by two-time Nobel laureate in chemistry and peace, Dr. Linus C. Pauling, in his landmark article on the mechanism of the cause of sickle cell anaemia published in 1949. He defined a new perspective on the origin of disease based upon the recognition that specific gene mutations can create an altered molecular environment, which therefore modified physiological function associated with specific diseases.
In 1950, Williams also coined the term “Genetotrophic Disease” to describe diseases which resulted from genetically determined nutritional metabolic needs not being met by the individual, and which result in poor gene expression. Patients with genetotropic conditions have increased needs of one or more nutrients in order to achieve normal physiologic functioning. These conditions respond favourably when enough of the required nutrients are provided. Many chronic diseases can be conceived as subtle genetotropic diseases, as long as nutrient supplementation fills a metabolic need to improve a patient’s condition. With this concept, Williams opened the eyes of the research and medical communities that expression of genes and therefore phenotypic function was modifiable through altered diet and nutritional status. He pointed out that human biochemical variation in function was much greater than nutrition and medicine recognized prior to his publications. The need for essential nutrients, which he referred to as “nutrilites” (i.e., vitamins, essential amino acids, and essential fatty acids), differs from the (average) daily amounts recommended for the general population.

The word “Orthomolecular” was introduced by Pauling in his seminal paper, Orthomolecular Psychiatry, published in 1968. Pauling defined Orthomolecular Psychiatry as the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the body. He later broadened this definition to include other diseases and amended it to “Orthomolecular Medicine,” which he defined as the preservation of good health and the treatment of disease by varying the concentrations in the human body of substances that are normally present in the body, and are required for health. The term, “orthomolecular” is used to express the idea of the right molecules in the right concentration. The key idea in orthomolecular medicine is that genetic factors affect not only the physical characteristics of individuals, but also their biochemical milieu. Biochemical pathways of the body have significant genetic variability and diseases such as atherosclerosis, cancer, schizophrenia or depression are associated with specific biochemical abnormalities which are causal or contributing factors of the illness.

Dr. Jeffrey S. Bland created the concept of “Functional Medicine” in 1991, which is a form of personalized medicine that deals with primary prevention and underlying causes, rather than only the symptoms, of serious chronic diseases. Functional medicine is anchored by an examination of core clinical imbalances that underlie various disease conditions. Those imbalances arise from environmental inputs, such as diet, nutrients (including air and water), toxins, exercise, and trauma together with a unique set of genetic predispositions, attitudes, psychological stress and beliefs. The core clinical imbalances that arise from malfunctions include: hormonal and neurotransmitter; oxidation-reduction and mitochondropathy; detoxification and biotransformation; immune; inflammatory; digestive, absorptive, and microbiological; and structural imbalances from cellular membrane function to the musculoskeletal system. Improving balance is the precursor to restoring health and it involves much more than treating the symptoms. Functional medicine is dedicated to improving the management of chronic disease by integrating the interventions at multiple levels to address these core clinical imbalances and to restore each patient’s functionality and health. Functional medicine is not a unique and separate body of knowledge. It is grounded in scientific principles and information widely available in medicine today, combining research from various disciplines into highly detailed yet clinically relevant models of disease pathogenesis and effective clinical management. Bland published a landmark book in 1999, Genetic Nutrioneer, in which he explains how proper nutrition and supplementation can modify genetic expression to create better health outcomes.

In 2006, Dr. Bruce N. Ames presented his “Triage Theory” of optimal nutrition that states that the human body prioritizes the use of vitamins and minerals when it is getting an
insufficient amount of them to be able to keep functioning.\textsuperscript{3} Triage means deciding which patients to treat when faced with limited resources. When faced with limited nutritional resources, the human physiology must decide which biological functions to prioritize in order to give the total organism and the species, the best chance to survive and reproduce. While short-term deficiencies or insufficiencies are common, they are often not taken seriously by mainstream physicians. Under such limited scenario, the body will always direct nutrients toward short-term health and survival capability and away from regulation and repair of cellular DNA and proteins that optimizes health and increases longevity. Dr. Ames's research shows how bodily insults accumulated over time as a result of vitamin and mineral insufficiencies and can lead directly to age-related diseases. The triage hypothesis states that the risk of degenerative diseases (associated with aging, including cancer, cognitive decline, and immune dysfunction), can be decreased by ensuring adequate intake of micronutrients.\textsuperscript{3,9-12}

"Metabolic Correction" is a functional term introduced by Drs. Michael J. Gonzalez and Jorge R. Miranda-Massari in 2011 to explain the mechanism of how nutrients are capable of correcting biochemical disruptions that promote the disease state.\textsuperscript{13} Metabolic correction embraces all these previously described biochemical/physiological concepts to explain how improvements in cellular biochemistry may help the body achieve metabolic or physiological optimization. Metabolic correction intervenes with impaired biochemical reactions that are associated with a lack of well being. In other words, metabolic correction is a fine tuning of the cellular physiology to improve function; therefore, preserving health, preventing tissue damage and reverting disease.

Why Metabolic Correction?
Inferior nutritional value of food and availability of nutrient dense foods

We need to eat a wide variety of food to obtain the substances we need. A big problem we face is that the nutritional values of foods that people eat seem to be greatly inferior to the listed values given in food tables. A study that assessed this issue showed declines in: protein (-6%), calcium (-16%), phosphorus (-9%), iron (-15%), riboflavin (-38%), and vitamin C (-20%).\textsuperscript{14} There is a dilution effect, in which yield-enhancing methods like fertilization and irrigation may decrease nutrient concentrations, an environmental dilution effect. Recently, evidence has emerged that genetically based increases in yield may have the same result, a genetic dilution effect. Modern crops that grow larger and faster are not necessarily able to acquire nutrients at the same, faster rate, whether by synthesis or from the soil. Today’s foods are not as nutritious as those eaten in the past. A report pointed out that US and UK Government statistics show a decline in trace minerals of up to 76% in fruit and vegetables over the period 1940 to 1991.\textsuperscript{15} The nutritional decline findings alone give reason to eat organic fruits and vegetables. In fact, for nearly all nutrients, organic fruits and vegetables remain the most nutrient-dense foods. This information makes the updated food pyramid not so much current as reflective of the need for an increase in fruits and vegetables in order to get the same nutritional benefits. Americans on average do not even come close to the recommendations to limit added sugars, refined carbohydrates, added fats and oils.

Adverse side effects of medication and iatrogenic deaths

There are more than 100,000 deaths annually due to medication properly prescribed and taken as directed.\textsuperscript{16,17} The incidence of serious and fatal adverse side effects in US hospitals is extremely high, as they are frequent and more so than generally recognized. Fatal adverse side effects appear to be the fourth leading cause of death in the US. If medication is necessary, providing metabolic correction principles may reduce medication requirement, reduce adverse side effects and improve outcome.\textsuperscript{13}
Compensate for the increased demand of nutrients due to the disease state
Burns lead to loss of protein and essential nutrients. Surgery increases the need for zinc, vitamin C and other nutrients involved in cellular-tissue repair. Broken bones need calcium, magnesium and vitamin C for healing. Infections challenge the immune system and place high demands on nutritional resources such as zinc, B-complex vitamins and vitamin C. The same nutritional demand is present when exposed to chemical, physical and emotional stress. Chronic disease sufferers are at higher risk of interactions between drugs and nutrients. There are thousands of conceivable genetic defects (inborn or acquired), so it is likely that many people have higher genetic requirements for many micronutrients. We need a better understanding of the interrelationship between nutritional biochemistry and the disease-pathological state.

Biochemical Mechanism of Metabolic Correction: Molecular Concentrations and Rate of Reaction
The majority of the chemical reactions that take place in living organisms are catalyzed by enzymes. The mechanisms of enzyme-catalyzed reactions in general involve: (1) the formation of a complex between the enzyme and a substrate, and (2) the breakdown of this complex to form the products of the reaction. The rate determining step is usually the breakdown of the complex to form the products. Under conditions such that the concentration of the complex corresponds to equilibrium with the enzyme and the substrate, the rate of the reaction is given by the Michaelis-Menten equation.

The rate of an enzyme-catalyzed reaction is approximately proportional to the concentration of the reactant, until concentrations that largely saturate the enzyme are reached. The saturating concentration is larger for a defective enzyme with decreased combining power for the substrate than for the normal enzyme. For such a defective enzyme the catalyzed reaction could be made to take place at or near its normal rate by an increase in the substrate concentration. This mechanism of action of gene mutation is only one of several that lead to disadvantageous manifestations that could be overcome by an increase in the concentration of enzymatic cofactors. These binding problems may result in metabolic inefficiency with the accumulation of metabolic by-products. In general, this is the Law of Mass Action as the vitamin and mineral concentration increases, enzyme efficiency increases. These considerations obviously suggest a rationale for Metabolic Correction where you provide the needed cofactors in the amount needed to improve function. This increased enzyme efficiency may allow a genetic defect to be overcome. This biochemical activity follows the chemical principle of Le Chatlier, which states that when stress is applied in an equilibrium situation; it will move to the direction to minimize stress. In this case there is an unfavourable equilibrium of active enzyme that with the addition of the necessary nutrients will be moved toward a more physiologically favourable metabolic state.

Many human genetic diseases due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which can partially restore the enzymatic activity. Several single nucleotide polymorphisms in which the variant amino acid reduces coenzyme binding and thus enzymatic activity can be remedied by raising cellular concentrations of the cofactor through high dose nutrient therapy.

Inadequate intakes of vitamins and minerals from food can lead to DNA damage, mitochondrial decay, and other pathologies. Ames suggests that evolutionary allocation of scarce micronutrients by enzyme triage is an explanation of why DNA damage is commonly found on micronutrient deficiency. Also, Motulsky has argued that many of the common degenerative diseases are the result of the imbalance nutritional intake with genetically determined needs.

As an example, folic acid and vitamin B₁₂ have an important function in the maintenance of nuclear and mitochondrial genome
integrity. Both in vivo and in vitro studies with human cells show that deficiency of these vitamins causes an array of problems in the nuclear and mitochondrial DNA which can be minimized with increased folate and cobalamin concentrations. In order to acquire the protective effect of these vitamins, they are needed in concentrations that are obtained at intake levels above the current recommended dietary intakes of folate (>400 µg/day) and vitamin B₁₂ (>2µg/day).²⁵

Chromosome breaks lead to mutations that precede tissue damage and disease. Many types of physiological impairments due to inadequacy of vitamins and minerals can lead to suboptimal organ-system function including poor drug metabolism, insufficient neurotransmitter production and impaired immune defences. Chronic vitamin-mineral undernutrition reduces immune competency and central nervous system efficiency; while increases morbidity which may lead to increases in degenerative diseases. This approach to optimize health by improving enzyme efficiency and thereby metabolism and physiology, is the basis of metabolic correction.

An example of metabolic correction is that high dose B vitamins can counteract a poor Km. As many as one-third of mutations in a gene result in the corresponding enzyme having an increased Km (decreased binding affinity) for a coenzyme, causing a lower rate of reaction.⁹,¹⁰ About 50 different human genetic diseases due to a poorer binding affinity of the mutant enzyme for its coenzyme can be remedied by feeding high dose B vitamins, which raise levels of the corresponding coenzyme; many polymorphisms also result in a lowered affinity of enzyme for coenzyme⁹ and thus may be in part remediable.

To summarize, metabolic correction has two important biological actions: (1) optimization of cellular function by improving enzymatic efficiency, and (2) producing a pharmacological effect to correct abnormal cell function due to biochemical disarray occasioned by the disease process. An optimum intake of micronutrients and metabolites, which varies with age, environmental factors and genetics, should tune-up metabolism and markedly increase health at a modest cost, particularly for the poor, obese, and elderly.¹⁰

**Ten Principles that Identify the Concept of Metabolic Correction in Disease Therapy**

1. Metabolic correctors, along with proper nutrition come first in medical treatment. Knowledge of the safe and effective use of the combination of nutrients, enzymes, hormones, and other naturally occurring molecules in their active forms, is essential to assure an effective outcome. However, some patients may need more acute treatment for their particular condition, for which pharmacological therapy is recommended.

2. Metabolic correctors have a low risk of toxicity. Pharmacological drugs always carry a higher risk and should be the second choice if there is a metabolic correction alternative available.

3. Some laboratory tests might be useful in identifying the nutritional needs of some patients these tests may not be readily accessible to all patients or may present certain limitations. In addition, some laboratory tests do not necessarily reflect nutrient and enzyme levels within specific organs or tissues, particularly in the nervous system. For many patients therapeutic trial and dose titration is often the most practical therapy approach, especially when utilizing synergistic metabolic correction formulations.

4. Biochemical individuality is a central precept of metabolic correction. Hence, the search for optimal nutrient combination doses is a practical issue. Doses of nutrients and their combinations above the recommended daily allowances are often effective. Many patients tolerate optimal doses and respond well; however, dose titration is indicated in otherwise unresponsive cases.

5. Recommended daily allowances of nutrients are intended for normal, healthy people. By definition, diseased patients are not normal or healthy and not likely to be adequately served by obtaining recommended daily allowances. Practically every person
is deficient or insufficient at some level due to an insufficient diet.

6. Environmental pollution of air, water and food is common. Diagnostic search for toxic pollutants is justified.

7. Optimal health is a lifetime challenge. Biochemical needs change and our Metabolic Correction prescriptions need to change based upon follow-up, repeated testing and therapeutic trials to permit fine-tuning of each prescription and to provide a degree of the best possible health outcome.

8. Nutrient-related disorders are always treatable and deficiencies and insufficiencies are curable. To ignore their existence is malpractice.

9. Genetic and hereditary disorders are often responsive to metabolic correction.

10. Inspire patients to realize that health is not merely the absence of disease, but the positive attainment of optimal function and well-being. This requires an active role of the individual in his lifestyle, and a commitment to continuous education along with a responsible attitude about health.

**Conclusion**

To encourage the most efficient metabolism, we need the basic macronutrients required for fuel, fat, protein and carbohydrate. But we also need 15 or so vitamins that are co-enzymes and 15 or so minerals that are required in enzymes, and then we need two essential fatty acids, omega-3 and omega-6, and also there are seven or eight essential amino acids. In addition, other important nutrients, such as coenzyme Q10, acetyl-L-carnitine, and lipoic acid, must be considered in our quest for physiological optimization. Virtually every metabolic pathway requires micronutrients.

What determines the optimal concentration of a nutrient is its physiological functionality. While most people function below 100% efficiency, they nevertheless do not present with any detectable disease or obvious (i.e., significant symptoms), yet we can improve their functionality if we supply them with the needed micronutrient substances in the optimum concentrations.

Certain individuals have a greater need than that supplied by the diet (even if on a good dietary regime). This could be caused by digestive problems, malabsorption, food sensitivities, metabolic dysfunction, low levels in neurotransmitter precursors, etc. This lack of needed micronutrient cofactors manifests insidiously and is difficult to identify. Some vague symptoms, such as lethargy, irritability, insomnia and difficulty in concentrating, may be present. Also, this affects the body’s ability to resist disease and infection, its ability to recover from exercise, surgery, disease, and the ability of the brain to function at an optimal level. Detecting and treating disease at its earliest stages of cellular biochemical abnormality, rather than waiting for clear clinical symptoms is cost effective and of benefit to the patient. Nutrient deficiency diseases are the end product of a long and complex series of nutrient depletion reactions. We need to abandon outdated paradigms of nutrient intake merely to prevent deficiencies and expand them to prevent chronic diseases and achieve optimal health with metabolic correction.

**Competing Interests**

The authors declare that they have no competing interests.

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Prevention and Treatment of Alzheimer’s Disease with Orthomolecular and Lifestyle Interventions

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Abstract Alzheimer’s disease (AD) is the most common form of dementia in the elderly. To date, there are no established therapies that slow or reverse the course of disease. Dozens of epidemiological associations exist between nutritional and environmental factors and the development of AD, but few studies have been done to explore whether modification of these risk factors changes the course of the disease. Affected individuals, their caregivers, and health care providers are left to choose between doing nothing and using unproven interventions. This review summarizes the orthomolecular and lifestyle interventions with the greatest benefit-to-risk ratio that are supported by the published medical literature.

Introduction

Alzheimer’s disease (AD) is the most common form of dementia in the elderly. This condition is characterized by a progressive loss of memory, increased apathy, and deterioration of a variety of intellectual functions. Emotionally and financially devastating to patients and their families, the disease affects every socioeconomic and ethnic group. North America has the highest reported incidence of dementia in the world, affecting a reported 6.4% of individuals >60 years old. Less than 2% of individuals in the same age group are affected in Africa, India, and south Asia. The disease increases dramatically with age with approximately 25% of the population older than 85 having significant cognitive impairment. Largely due to the aging baby boom generation, the annual total number of new cases of AD is projected to double by 2050.

The prevention and management of AD with orthomolecular and lifestyle interventions is as much about the strategy as it is about the agents being used. Philosophically, the goals of natural therapeutics in AD consist of prevention, disease stabilization and reversal, as well as symptom management. The nature of the disease does not lend itself well to study. Plenty of epidemiological associations exist, but few studies have been done to explore whether modification of the risk factor changes the course of the disease. Individuals are left to choose between doing nothing and using unproven interventions. This review will briefly summarize the orthomolecular and lifestyle interventions with the greatest benefit-to-risk ratio that are supported by the published medical literature.

Pathology

With age, all brains exhibit some degree of degeneration, but the process is accelerated in AD. An accumulation of protein deposits, inflammation, and loss of both structure and function are hallmarks of the disease pro-
cess. In the brain, the protein deposits accumulate and form neurofibrillary tangles and amyloid-β (Aβ) peptides. The presence of these plaques and tangles have been correlated with the clinical disease, but there is significant debate as to whether plaques and tangles directly cause damage, or are simply by-products of another process.5

In AD, the cerebral cortex, basal forebrain, and other areas of the brain have fewer synapses, fewer synaptic proteins, and reduced membrane phospholipids, which are essential for cell stability.6 The maintenance of appropriate lipid membrane content may prevent the production of Aβ peptides and subsequent neurodegeneration.7 The nerve cells that are particularly affected are those that are stimulated by the neurotransmitter called acetylcholine (ACh). Current pharmaceutical therapies strive to increase the availability of ACh throughout the brain. Overall, there is significant wasting of brain tissue.

Functionally, the AD brain exhibits abnormal glucose metabolism, which is in accord with the findings that diabetes, another disease of impaired glucose metabolism, is an independent risk factor for AD. This ‘brain hypometabolism’ is especially evident in individuals with a maternal family history of AD and in carriers of AD-related genes.8

Economics

In US dollars, AD cost an estimated $183 billion in 2011, and this cost is predicted to increase to $1.1 trillion in 2050. Because most people with AD are over age 65, Medicare and Medicaid cover approximately 70% of these costs. Individuals with AD cost Medicare almost three times as much as the same-age individuals without AD. As the incidence of AD continues to rise, there is a tremendous financial incentive to preventing and slowing the degenerative process.9

Signs and Symptoms

The inability to remember new information is typically the earliest manifestation of AD. Other symptoms include confusion, difficulty solving problems, problems with spatial relationships, problems speaking or writing, poor judgment, social withdrawal, or mood changes.9,10 Depression occurs in approximately 50% of individuals with AD.2 Death usually occurs as a result of AD-related pneumonia due to the affected individual’s lack of mobility.9

Clinicians use diagnoses of “possible AD” or “probable AD,” but pathological confirmation via autopsy is required for a diagnosis of “definitive AD.” This classification system poses notable challenges for the study of early disease, as the clinical diagnosis is not always in agreement with the brain pathology and autopsy findings represent a late stage of disease.

Risk Factors

Age is the single greatest risk factor for developing AD, but it is not an inevitable course of aging. The disease is thought to be due to a combination of genetic and environmental risk factors.

Mild Cognitive Impairment (MCI) is a condition in which an individual experiences cognitive dysfunction severe enough to show up on cognitive tests and to be noticeable to others, but not severe enough to interfere with activities of daily living.9 MCI is an established risk factor for the development of AD, although not all individuals with MCI will develop AD. The diagnosis of MCI may represent a window of opportunity for intervention, should neuroprotective intervention strategies prove useful in larger scale trials.

Genetic Associations

At least six different genes have been linked to the development of Alzheimer’s,2 all of which result in the accumulation of protein debris described above. Individuals with a parent or sibling with AD are at increased risk of developing AD, and this risk goes up with each affected family member.9 Globally, Africa has the lowest reported incidence of AD2 and studies support the idea that being of African descent appears to offer some protection against the disease.11

The most well-established susceptibility gene for late-onset AD is the APOE gene, which is involved in cholesterol trans-
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The gene comes in three forms, APOE-2, -3, and -4. Individuals who inherited the APOE-4 allele from one parent have a 2 to 3-fold risk of developing AD, and six to seven years earlier, than those without the gene. Inheritance of two copies of the gene (from both parents) results in a 5-fold risk of developing the disease. Possession of APOE-4 has been associated with dysfunctional carbohydrate metabolism in the brain, and a more pro-inflammatory state, two established components of AD. Depending on the geographic region, between 37% - 64% of individuals with AD possess the APOE-4 allele, with the most significant association between APOE-4 and AD found among individuals in northern Europe. While the risk of developing AD is significantly greater among individuals with one or two copies of the APOE-4 allele, not all of these individuals will develop the disease.

Modifiable Risk Factors

Each of the following is a modifiable risk factor. An individual has some influence over whether or not they have the risk factor, or the degree to which they have it. Unfortunately, few randomized controlled trials have been completed to determine whether modification affects outcome. If a patient already has AD, does changing the associated risk factors change the rate of progression of the disease? Such studies are complicated and expensive, and yet to be conducted. Since no known therapies exist to slow or reverse the disease, a reasonable strategy is to avoid the things that have been associated with disease and encourage those that have been associated with prevention.

1. Environment

Pesticides: An ecological study evaluated the relationship between environmental exposure to pesticides and the development of neurodegenerative diseases. It showed an increased risk for AD in districts with greater pesticide use.

Aluminum: There have been repeated epidemiological correlations between aluminum (Al) exposure and the incidence of AD, with some studies showing a dose-response relationship. An established neurotoxicant, Al appears to promote AD progression. While mechanisms explaining the connection have not been fully elucidated, Al has been shown to be associated with a significant increase in markers of inflammation and the formation of plaques in animal models of AD. Individuals with a diagnosis of probable AD have significantly higher serum levels of Al than healthy individuals or those with dementia from other causes. Al exposure comes from a variety of sources including deodorants, antacids, water, and food. The most significant of these sources is likely water, where Al compounds are used in many municipal water supplies as a means to purify the water from microorganisms. Thirteen studies and a meta-analysis have established an association between the incidence of AD and the Al concentration in the municipal drinking water.

2. Cardiovascular Disease and Diabetes

Metabolic Syndrome, or Syndrome X, refers to a group of related conditions plaguing the Western world. The syndrome includes abdominal obesity, insulin resistance/ type 2 diabetes, high blood pressure, and elevated blood lipids. The syndrome, presumably associated with a high carbohydrate diet and consumption of refined sugar, is associated with increased risk of stroke, heart attacks, as well as the development of AD. Mounting evidence suggests a cholesterol defect may be involved in AD, and that elevated blood levels of LDL may be an attempt at delivering cholesterol to the brain. Cholesterol is an important brain nutrient where it insulates neurons, aids communication between cells, and acts as an antioxidant. When cholesterol cannot reach neurons, free radicals are produced, resulting in abnormal cell function and eventually cell death.

3. Homocysteine

Elevated homocysteine is a recognized risk factor for cognitive impairment and AD. Homocysteine levels increase due to
a deficiency of B-vitamins, which have been shown to be low in patients with AD. When researchers conducted a 2-year study of B-vitamin supplementation on AD progression, they found reversal of early cognitive impairment among individuals with elevated (>11.3 µmol/L) homocysteine. Most notable was a 69% higher likelihood of correct word recall compared with placebo after 2-years supplementation. The therapeutic use of homocysteine-lowering vitamins (i.e., B₆, B₁₂, folic acid, betaine, and choline) should be able to maintain homocysteine levels below 10 µmol/L, and mitigate this risk factor.

**Dietary Interventions**

The Mediterranean diet: The Mediterranean diet (MeDi) refers to the diet traditionally consumed throughout Southern Europe, near the Mediterranean Sea. The diet is high in plant foods, including vegetables, fruits, grains, beans, nuts, and seeds. Fish, poultry, dairy, and red wine are consumed in low-to-moderate amounts, and red meat consumed infrequently. The major source of fat in the MeDi comes from olive oil and the diet is low in saturated fat overall. The diet has been associated with reduced incidence of AD and related cardiovascular diseases. It is unclear if there is a particular nutrient or combination of nutrients that confers protection.

A well-conducted study in Greece sought to determine whether dietary and lifestyle variables affected cognitive function in the elderly. The researchers found that adherence to the MeDi were not found to be associated with cognitive function. Rather, physical activity and height were associated with improved cognitive performance whereas increased risk of dementia was associated with depression, diabetes, and age.

A large study, The Chicago Health and Aging Project (CHAP), found an association between intake of saturated fat and cognitive decline. Alternatively, unsaturated oils from plants were shown to be protective against age-related cognitive decline and AD in large longitudinal studies conducted throughout Europe. The findings from the CHAP study also support a role for unsaturated oils, as they found that frequent consumption of fish, a rich source of polyunsaturated oil, was associated with better cognitive function. Individuals who ate fish at least once weekly had cognitive scores decline about 10% more slowly than those who avoided fish.

**Low-carbohydrate diet:** AD is associated with insulin resistance, elevated cholesterol, and obesity. It should come as no surprise that AD has been termed “type 3 diabetes.” Elevated sugars interfere with the brain’s ability to access essential fats and contribute to insulin resistance.

**Nutrient-dense foods:** Epidemiological studies have shown that individuals who consume diets high in antioxidants are afforded cognitive protection. Cherries, grape juice, berries, and walnuts have been shown to enhance resistance to oxidative stress and improve verbal memory performance. Curcumin is isolated from the spice turmeric, often used to make yellow curries and mustards. Its antioxidant properties are especially suited for the brain. Studies in mice demonstrate curcumin decreases inflammation and reduces oxidative damage in the brain.

**Orthomolecular Interventions**

**Omega-3 Fatty Acids:** The omega 3 polyunsaturated fatty acids are major constituents of neuronal lipids, and docosahexanoic acid (DHA) is thought to be the most neuroprotective form of fat. DHA has been shown to improve membrane fluidity, decrease inflammation, prevent oxidative damage, reduce tau aggregation, discourage amyloid formation, improve signal transduction, and facilitate neural re-growth.

A randomized controlled trial of 2 grams of DHA daily for 18 months did not slow the rate of cognitive decline in patients with mild to moderate AD. It was suggested that a year and a half of DHA supplementation does not accurately replicate the effects of a lifetime of fish consumption. In addition, this protocol neglected to include other nutrients found in seafood, such as trace minerals, which may account for some of the protection afforded by fish consumption in epidemiological studies.
Based on current evidence, oily fish should be consumed several times per week. Sardines, pickled herring, and smoked salmon (lox) require no preparation and can be found relatively inexpensively. Fish oil supplements are widely available and should be considered, although the ideal dose has not been determined. Daily doses as high as 4,000 mg of DHA may be required.

**Creatine**: Creatine is a naturally occurring nitrogenous organic acid that plays an essential role in cellular energy supply. It is manufactured endogenously from L-arginine, glycine, and L-methionine and therefore not considered an essential nutrient. That brain energy capacity may influence cognitive performance has led to the hypothesis that supplemental creatine may have therapeutic value in the treatment of dementia. This idea is supported by the findings that brain creatine levels, measured via magnetic resonance spectroscopy, have been shown to be associated with some aspects of memory.

Animal muscle is the primary source of dietary creatine, putting vegetarians at risk for deficiency. While vegetarians have been shown to have significantly lower creatine levels in skeletal muscle than omnivores, brain differences among these groups has not been reported. Two studies have examined the effects of creatine supplementation on cognitive function in vegetarians. The first demonstrated that 5 g/day of creatine supplementation had a significant positive effect on two cognitive tests measuring processing speed. In the second study, the authors concluded that 20 g of creatine supplementation for five days resulted in improved memory for vegetarians, but not omnivores. In this short trial, supplementation did not influence measures of verbal fluency or vigilance.

In young adults, 0.03 g/kg/day of creatine supplementation did not improve cognitive processing after six weeks of supplementation. In the elderly, however, 5 g creatine four times daily did result in improvement of four of five cognitive tasks measured. The authors concluded that creatine supplementation was effective for enhancing cognitive function in the elderly.

Unfortunately, cognitive enhancement research does not necessarily translate into AD therapeutics. Both creatine and creatine kinase (CK), the enzyme responsible for the conversion of adenosine triphosphate to adenosine diphosphate, have been shown to be reduced in the brains of individuals with AD. In one study CK activity was 86% decreased in brain homogenates of patients with AD compared to age-matched controls. While researchers have suggested that administration of creatine may prevent or delay the course of AD-related neurodegeneration, such a randomized controlled trial has not been conducted and it is difficult to predict whether the AD-specific decreases in creatine and CK may influence response to supplementation.

**Physical, Mental, and Social Activity**

**Stress**: A lifetime study of clergy members in the Catholic Church found that those exposed to high levels of chronic psychological stress were more than twice as likely to develop Alzheimer’s as those with low levels of psychological stress. It is known that high levels of cortisol negatively impact the hypothalamus, which is a center of learning and memory. Chronic stress is associated with metabolic and inflammatory changes that are thought to favour the development and progression of AD. In clinical studies, high exposure to stress was associated with cognitive impairment among APOE-4 positive individuals.

**Exercise**: Several studies have demonstrated that physical activity is associated with improved cognitive performance and reduced risk of AD. Even among individuals who already have AD, a 12-week program that included training in balance/coordination, joint mobility, resistance, and flexibility resulted in significant improvements in physical outcome measures and the individuals’ abilities to independently perform activities of daily living. In addition to the purported benefits of enhanced blood flow to the brain, physical activity has been demonstrated to offer protection against the body’s response to stress.
Social Activity: Withdrawal from social activities is a symptom of even mild stages of AD. A group of Finnish researchers studied the effects of social stimulation on cognition in elderly individuals suffering from loneliness (individuals in this study did not have AD). In this randomized, controlled trial of 235 participants, individuals were exposed to active discussions and therapeutic writing, group exercise, or art experiences over three months. The study concluded that psychosocial group intervention improved cognition in lonely elderly individuals.

Conclusion

While the personal, social, and economic impact of AD are enormous, and a growing public health concern, few current conventional interventions offer prospects for prevention or long-term cognitive benefit. Orthomolecular and lifestyle interventions may have an important role in both the prevention and treatment of AD. Unfortunately, only a few rigorous clinical trials have been conducted to determine the safety or efficacy of several orthomolecular interventions. Furthermore, these therapies may well work in concert with one another (e.g., fish oils and dietary antioxidants), but do not lend themselves well to standard clinical trial methods. For these reasons, epidemiological studies give us clues as to what may be protective from developing dementia and/or AD.

From these studies, we know that lifestyle modifications are the most likely avenue to maintain cognitive function. These include: daily exercise (physical and mental), social involvement, attention to dietary patterns, and avoidance of known environmental risk factors. While it is easy to list these, it is well-known in medicine that lifestyle modifications are difficult for patients to adopt. Rather than a single therapy that offers a cure, it is likely that the best way to slow, stop, or reverse AD will be through a holistic combination of many interventions. There are virtually no risks to increasing one’s physical and social activity, and improving diet to include nutrient-dense foods (beans, nuts, vegetables, oily fish) and fewer carbohydrates. All patients, and their families, should be encouraged to adopt these habits to the greatest extent possible. While some orthomolecular interventions are supported by preliminary data and have promise in the management of AD, more study is certainly needed with respect to optimal dosing, brand, and the potential interactions with other medications. Overall, the orthomolecular and lifestyle interventions reviewed here are supported by the published medical literature, have few side effects, and, pending more clinical research, have tremendous potential for neuroprotection in AD.

Competing Interests

The author declares that she has no competing interests.

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The Niacin Flush Pathway in Recovery from Schizophrenia and how Arginine and Glutamine may Provide Added Benefit

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Abstract A reduced niacin-mediated flush is increasingly accepted today as a positive diagnostic indicator for schizophrenia. Schizophrenics that were successfully treated with high dose niacin (nicotinic acid) therapy by Dr. Abram Hoffer in the 1950s recovered from their otherwise previously reduced flush response simultaneous with recovery from schizophrenia. Significantly, some schizophrenics also recovered after high dose nicotinamide treatment, a different nicotinamide adenine dinucleotide (NAD) precursor that does not cause a flush response. Whether the niacin-flush response is first due to replenishment of NAD deficiency or due to a restoration of polyunsaturated fatty acid levels thus restoring niacin-flush competence is not mutually exclusive. It is possible that nicotinic acid is first dedicated to intracellular NAD synthesis at the expense of the flush response until the schizophrenic’s immediate needs for NAD are finally met. Then the nicotinic acid, rather than entering the cell through transporters, instead becomes available to bind GPR109a, on the surface of the cell thus mediating the flush pathway. Moreover the restored NAD levels may also revive the biosynthetic pathway required for generation of the known niacin-flush vasodilatory molecules PGD2, PGE2, PGI2, and thromboxane A2. The schizophrenic patient may potentially benefit by additional supplementation with arginine to aid in restoration of the vasodilation, and glutamine to increase NAD synthesis. Arginine increases the amount of nitric oxide (NO) synthase substrate available towards more sustained niacin-NO-vasodilation pathways, while glutamine increases the amount of required substrate available for conversion of nicotinic acid adenine dinucleotide to NAD. The addition of these two amino acids with high-dose niacin therapy has the potential to provide significant additional therapeutic benefits when treating schizophrenia, especially the chronic cases.

Introduction Nicotinic acid (commonly known as niacin) is largely used for controlling dyslipidemia. Niacin raises high-density lipoprotein (HDL) to a greater extent than any known cholesterol-associated drug while also lowering triglycerides, total cholesterol, and very-low-density lipoprotein. However, there are many more uses for niacin, which have been overlooked by conventional medi-
cine in spite of clinical proof and repeated anecdotal evidence, perhaps in part because many other therapies are not as clearly quantifiable. Nonetheless, the amazingly varied benefits of niacin treatment are actually to be predicted. Niacin serves as a precursor to endogenous biosynthesis of nicotinamide adenine dinucleotide (NAD), a molecule that is required in a greater shear number of protein catalyzed reactions than any other vitamin-derived molecule (>450 reactions). NAD as a part of NAD, NADH, NADP, or NADPH is essential to all life ranging from bacteria to man. NAD functions in most biochemical homeostasis: catabolic and anabolic. Dietary precursors to NAD are termed vitamin B3. Similarly, the observation that niacin helps with a wide variety of therapeutic benefits is unsurprising because the most devastating dietary deficiency disease ever observed naturally occurring in modern human history were the pellagra epidemics that happened just after the development of milling technology that would introduce white rice and flour to the masses. Over 125,000 United States southerners would die due to pellagra in just the first two decades of the 20th century! This all indicates the human animal’s particularly great susceptibility to NAD deficiency arising from unfortunate dietary habits.

Schizophrenia, however, seems likely to involve an even greater susceptibility to NAD deficiency states due to genetic reasons. Entire mental asylums in the United States were full of pellagrins with dermatitis during the height of the epidemics of the 1920s. Shortly after the discovery of niacin in 1939, the government began the mandatory fortification of bread, flour, and rice. By the 1950s, Drs. Abram Hoffer with Humphry Osmond experimented with using niacin as a means of treating schizophrenics. This was initiated based on the observation that pellagrins so resembled their schizophrenic patients. Hoffer had originally been a PhD that was studying fortification of grains. Then he decided to become a MD after becoming frustrated with the lack of respect he was receiving regarding his fortification recommendations. Together, Hoffer and Osmond would discover that treating acute schizophrenics with gram quantities of niacin or niacinamide frequently resulted in dramatic complete recoveries from the disease. So the theory was born that perhaps acute schizophrenics have a greater genetic dependency for niacin. Today this theory remains plausible. Hoffer treated over 10,000 patients using gram quantities (typically 3g) of niacin or niacinamide (nicotinamide). Most interestingly, he discovered that schizophrenics do not flush as much as non-schizophrenics. Since Hoffer’s discovery other investigators have repeatedly confirmed his observation of reduced flush response in multiple studies published within our current decade (this is just a sampling).

Most interestingly, Dr. Hoffer observed complete recovery of his patients from acute schizophrenia after high-dose niacin treatment. However chronic schizophrenics frequently did not recover after niacin treatment. Similarly, first episode schizophrenics have a reduced niacin flush response, while reduced niacin flush is not observed with multi-episode schizophrenics. Now niacin skin flush-based diagnostic tests are being developed and marketed. Moreover entire expensive investments into genetic studies based on the flush response phenotype are being performed to better understand this quantifiable phenotype.

In this article, we describe the signal transduction pathway starting from ingestion of nicotinic acid and proceeding to the physiological flush response, while relating this to schizophrenia. In the end we find that there are still significant gaps in our understanding of these pathways, but that additional supplemental strategies are predicted to potentially improve the weakened schizophrenia pathways, thus possibly promoting recovery. Novel therapeutic emphasis is placed on fulfilling these rate-limiting molecules to support recovery from schizophrenia-associated NAD/vasodilation-deficits. Specifically, this involves high doses of arginine and glutamine, since these combinations have the potential to exert therapeutic benefits in the treatment of acute schizophrenia and perhaps even among chronic schizophrenia.
Nicotinic Acid Pathways to Vasodilation and NAD

The niacin-mediated flush response is well known to be reduced in schizophrenic patients. Conversely, recovery of the flush response has been directly correlated with recovery from acute schizophrenia. The flush is first evidenced in the skin by a redness that is sometimes accompanied with an itchy sensation and perceptibly noticeable changes in body temperature as the warm blood moves more distal. A slight flush response is most therapeutically desirable for correcting dyslipidemia (either too high or too low cholesterol/lipids) – no flush is observed with high dose niacinamide treatment and no correction of dyslipidemia is observed either.

In order for the suffering schizophrenic to optimally benefit from the modern understanding of the niacin-flush, we must consider both of these distinct separate pathways starting from nicotinic acid and going either: (1) Straight to the intracellular synthesis of NAD; or (2) To the membrane-activated nicotinic acid-mediated flush response. Here, we focus on NAD biosynthesis. While nicotinic acid serves an essential function as dietary precursor used for biosynthesis of NAD, there are also several other dietary precursors to NAD. However, none of these cause a flush response. These are nicotinamide (commonly known as niacinamide or no-flush niacin; NAM), tryptophan (W), or nicotinamide riboside (NAMR). In order to make NAD starting from niacin, your body also requires thiamine for making phosphoribosylpyrophosphate, (PRPP). This PRPP combines with nicotinic acid in the first reaction to make nicotinic acid mononucleotide. Then, ATP is needed to make nicotinic acid adenine nucleotide (NaAD). Finally, glutamine is required to convert the nicotinic acid to nicotinamide, thus creating NAD and liberating glutamate. The therapeutic benefits of increased NAD are nearly incomprehensible and limitless given NAD’s role in general cellular metabolism and energetics. The specific potential therapeutic effects of additional glutamine supplementation are considered in the next section.

Of the NAD precursors, nicotinic acid is uniquely distinguished as the only NAD precursor for which there is a specific high affinity G-protein coupled receptor, GPR109a and GPR109b (Figure 1, p.35; upper & right boxes). Tremendous advances in our basic understanding of the molecules involved in the nicotinic acid flush pathway have been made just over the past decade. The pathway from nicotinic acid to flush response involves multiple ligand:g-protein coupled receptor interactions, multiple secondary signaling molecules, and several different specific tissues. At the end of the signal transduction pathway from niacin to physiological flush response, there are two distinct pathways, both of which converge to promote vasodilation. These are briefly a niacin-mediated massive release of prostaglandins, and a niacin-mediated increase in endothelial nitric oxide synthase (eNOS/NOS3) expression. The former pathway has been much more actively studied. Nicotinic acid activation of the nicotinic acid G-protein coupled receptors GPR109a and GPR109b leads to a massive release of a wide array of prostaglandins (PGD-PGH) from a combination of dendritic cells (Langerhans) and keratinocytes. The vasodilatory molecules PGD2, PGE2, PGI2, and thromboxane A2 are all increased after niacin treatment. PGE2, PGD2, and PGJ2 are most appreciated currently, where PGD2 is believed to exert the most dramatic flush response effects. PGE2 and PGD2 bind to specific G-protein coupled receptors (GPR109a and GPR109b) on other cells, while PGJ2 binds to and activates the nuclear transcription factor, peroxisome proliferator-activated receptor gamma, the drug target of the thiazolidinedione class of drugs used to control lipodystrophy/diabetes.

Niacin increases phosphorylation of eNOS to increase its half-life in the brain. Here eNOS promotes angiogenesis so critical to stroke recovery. Endothelial NOS controls basal vascular dilation. Elimination of eNOS does not prevent overt niacin flush in mice studies, thus suggesting a mi-
nor role for eNOS in niacin-mediated flush response. Nonetheless, we still expect a role for niacin-eNOS-dilation that may even be more sustained but less acutely intense. The nitric oxide enzyme requires arginine for production of nitric oxide, which also increases vascular dilation. In fact vasodilation can overcome erectile dysfunction where viagra/sildenafil work via increasing nitric oxide production. Most interestingly, the addition of niacin and arginine to PED5 inhibitors like viagra has been shown to improve sexual satisfaction. HDL stimulates NO production through eNOS, and no other drug increases HDL more than niacin. This seems likely to promote vasodilation in the brain that is perhaps crucial to its varied benefits to mental health. Niacin has been shown to decrease inducible nitric oxide synthase isoform (iNOS) expression, where iNOS activity is associated with inflammation and eNOS activity is associated with vascular dilation via endothelial relaxation. As a means of increasing the desired flush response in schizophrenics, it makes sense to also consider using arginine since it is the substrate used by nitric oxide synthase. In the end both the prostaglandin-GPCR-cAMP-PKA and the NOS-NO pathway converge to dephosphorylate the contractile protein myosin light chain kinase that ultimately mediates the mechanics of vasodilation. The two substrates, glutamine and arginine are discussed later in the manuscript as potentially useful additions to high dose niacin therapy for treating acute and possible chronic schizophrenia.

Explanations for the Simultaneous Recovery from Acute Schizophrenia and the Niacin-Flush Response

Hoffer observed that treatment with high doses of the non-flush NAD precursor, nicotinamide, also frequently resulted in recovery from acute schizophrenia similar to recovery from pellagra dementia. While restoration of the nicotinic acid-mediated flush response does correlate with niacin-mediated recovery from schizophrenia, it does not necessarily mean that this effect was primarily the result of the flush response. It seems much more likely that the restoration of NAD levels is central to recovery, where NAD as NAD+, NADP+, NADH, and/or NADPH, may be restoring prostaglandin-flush pathways by one or a combination of the >450 reactions that require NAD for activity. There are several possible explanations for the observed reduced flush response. In this section we give consideration to each explanation and ultimately come to the conclusion that the reduced flush response is firstly an NAD deficiency, where PUFA reductions are likely to be secondary to this effect. This analysis concludes that schizophrenia is most likely not an essential fatty acid deficiency disease, but more of a NAD deficiency disease.

Firstly, the reduced niacin flush response observed in schizophrenia likely involves niacin receptor ligand mediated desensitization. A metabolic study of schizophrenia indicates a general increase in PUFA catabolism. Beta-hydroxybutyrate levels were found to be elevated 2.6 fold. Beta-hydroxybutyrate is proposed to be the naturally occurring endogenous ligand for the high affinity nicotinic acid G-protein coupled receptor. Decreased levels of the GPR109a protein are observed in the brains of schizophrenics, as increased GPR109a transcripts. Such ligand dependent receptor down-regulation (a.k.a., receptor desensitization) is a common theme with the G-protein coupled receptor protein superfamily. Thus, NAD may be simply restoring PUFA metabolism such that the levels of the beta-hydroxybutyrate ligand for the high affinity nicotinic acid G-protein coupled receptor are returned to normal levels. The GPR109a protein may then be expressed at correct levels, thus restoring the niacin-flush response to normal as well. This general alteration is surely a major contributor to the reduced flush response seen in schizophrenics.

Prostaglandins are synthesized starting from arachidonate - the predominant PUFA. Thus it would make perfect sense if arachidonate levels were reduced in schizophrenics resulting in a reduced flush response. However, metabolite studies of schizophrenia
indicate that arachidonic acid levels are not altered in schizophrenia. Instead, increased levels of the related molecule, adrenic acid (2 carbons added to arachidonate, i.e., 22:4), are inversely correlated to the niacin flush response, with its levels being elevated in schizophrenics by 20%. This means that the rate of elongation for arachidonic acid is severely altered in schizophrenics. Elevated adrenic acid has also been correlated with diabetes incidence in schizophrenics and also in patients with increased schizotypal personality traits. Adrenic acid is a curious molecule with higher levels occurring in early development, but then reduced levels with aging. Decades ago adrenic acid research determined that it was metabolized to dihomoprostaglandins by cyclooxygenase. More recent research confirms this finding, but the activities and physiological significance of this remains to be determined. It appears that the increased adrenic acid might compete with arachidonate. Moreover, the dihomoprostaglandins produced from adrenic acid may then interfere with the other prostaglandins, which clearly has the potential to interfere with prostaglandin-dependent inflammatory pathways and perhaps mental health. We simply do not know.

Another potential contributor to the reduced flush may involve hyper-delivery of nicotinic acid to cells at the expense of nicotinic acid availability for binding the nicotinic acid receptor. In other words, the schizophrenic individual is particularly deficient in NAD and thus a greater amount of nicotinic acid is quickly soaked up by cells for use in NAD synthesis, thus leaving less extracellular nicotinic acid available for activation of the GPR109-flush response pathway. Once the needs for NAD synthesis are satisfied, then the nicotinic acid becomes available to cause the flush response, as was observed in Hoffer’s recovering schizophrenics. This explanation does not seem likely to be the major contributor of the reduced flush response based on metabolic studies, but it may in part contribute to a reduced flush response.

Finally, whether the nicotinic acid effect on schizophrenic physiology is in part due to increased delivery of NAD to hard to reach critical brain tissues or to some other unique aspects of schizophrenic physiology is unknown. We do not even know whether niacin causes dilation in the brain blood vessels, but with the known increase in brain endothelial nitric oxide expression, we assume this is the case. The majority of basic niacin research has been focused on cardiovascular disease/lipid profiles, and not on mental disease/brain tissues. More research should be dedicated to understanding the niacin-flush response biochemistry as related to schizophrenia. In summary, the data suggests that schizophrenia is more of a NAD deficiency disease than an essential fatty acid deficiency disease.

**Potential Additional Benefits with Glutamine and Arginine**

Hoffer’s positive results with high dose niacin treatment were primarily limited to cases of acute schizophrenia. Chronic schizophrenics generally did not recover. Perhaps something else in the pathway from niacin to NAD and/or the flush response is limited in the more chronic schizophrenic that has not completely suffered an otherwise apparently irreversible neurodegenerative fate. Assuming schizophrenia is primarily a NAD deficiency disease that is particularly responsive to high doses of nicotinic acid, what other molecules may be rate-limiting in this pathway to recovery? What is the practical import of the current knowledge of the niacin-mediated flush biochemical pathways? On first glance of these pathways, it appears that glutamine and arginine are potentially therapeutic molecules worthy of greater consideration in treating schizophrenia.

Glutamine is required for the last step in the conversion of niacin to NAD when starting from either tryptophan or nicotinic acid/niacin (Figure 1, p. 35). Glutamine is a conditionally essential amino acid for uncertain reasons. It is particularly important in proliferating tissues, where gliomas have been described as “addicted” to glutamine. Undoubtedly, this means that glutamine is essential to some cancer cells and other nor-
mal proliferating cells. Interestingly enough, transformed cancer cells are well known to be exceptionally dependent on high NAD levels. In fact, chemotherapy is one of the most common situations today where the NAD deficiency disease pellagra is actually recognized and diagnosed in the clinic. There are several chemotherapeutics currently being considered that specifically cause NAD depletion via inhibition of either the rate limiting enzyme for conversion of nicotinamide to NAD or they target the rate-limiting enzyme in the pathway-mediated conversion of tryptophan ultimately to NAD (indoleamine 2,3-dioxygenase; IDO). IDO is exceptionally highly expressed specifically in tumor cells. The conversion of tryptophan to NAD ultimately requires the presence of glutamine in the final step. Since IDO inhibitors have repeatedly been shown to kill tumor cells, IDO is today a very exciting and active molecular target focus area in chemotherapeutic research. In summary, many cancer cells are known to essentially require high IDO activity, high NAD levels, and glutamine levels. Since glutamine is required for the IDO-mediated conversion of tryptophan to NAD, it is highly likely that glutamine plays an important role in facilitating the completion of the conversion of tryptophan to NAD in proliferating cells in general. Crude pharmacologic data supports a role for the alpha-ketoglutarate bioenergetic pathway of glutamine in gliomas. However, the former possibility for a role of glutamine specifically in the production of NAD starting from tryptophan is unexamined. Furthermore, the fact that this addiction to glutamine is seen in a form of brain cancer makes one wonder whether there are similar important roles related to schizophrenia since it can also be considered a disease of the brain. The bottom line is that glutamine is almost certainly essential to certain types of brain cells perhaps due to glutamine’s role in the synthesis of NAD starting from nicotinic acid or tryptophan. Ultimately, the addition of glutamine to a high doses regimen targeting schizophrenics may thus provide additional therapeutic benefit.

If the niacin-mediated flush response is most important in recovery from schizophrenia, then additional supplementation with arginine, the substrate used by the nitric oxide enzymes to begin nitric oxide-mediated vasodilation, may provide added therapeutic benefit. Arginine is well known to promote vasodilation during exercise or hypercholesteremia. Niacin increases brain endothelial nitric oxide synthase protein expression which is known to cause increased basal vasodilation and angiogenesis. Thus it would be reasonable to include additional arginine to sustain the vasodilation. Nitric oxide physiology is quite complicated. NO is involved in many physiological processes. NO is most well known for its roles in fighting infections, vasodilation as opposed to vasoconstriction, and poorly understood neurological roles including neurotransmission/gastrotransmission. There are three nitric oxide synthase genes that are regulated at the transcriptional level to express their respective proteins in specific tissues. These three genes are the neuronal (nNOS/NOS1), inducible (iNOS/NOS2), and endothelial (eNOS/NOS3), which are expressed respectively in vascular endothelial cells, neural tissues, and immune cells. The inducible nitric oxide synthase isoform is made particularly in response to infection, environmental toxins, and a variety of other stimuli. In this role, NO functions as a highly reactive molecule in killing microbes. NO radicals are elevated as measured post-mortem brains of schizophrenics. Given the complex roles of iNOS, nNOS, and eNOS, it is difficult to say which one is contributing to the observed increase in NO. If schizophrenia is a disease involving brain inflammation, then perhaps iNOS activity is dysregulated and causes excessive production of nitric oxide. In fact, studies do reveal a dramatic increase in expression of the glial inflammation-associated protein S100b in schizophrenics, thus supporting the idea that the increased nitric oxide observed in schizophrenic brains is most likely due to increased iNOS activity, but not so much changes in eNOS or nNOS. The role of eNOS in cardiovascular health is well known and studied intensely particularly as
related to the disease of atherosclerosis, while the role of nNOS is less understood with respect to various diseases. By supplementing with arginine, we can potentially increase vasodilation, circulation, delivery of NAD precursor, and angiogenesis. Whether this is likely to help in schizophrenia is unknown but given that there are few reported side effects for high doses of arginine or glutamine it seems there is little to risk with potentially much to gain by including these two amino acids in any high dose niacin therapeutic approach to treating schizophrenia.

**Dosage**

The average US diet provides 4–5 g of arginine a day. Cardiovascular benefits are clearly observed in clinical trials when providing additional supplementation of 3–10 g three times daily. High doses have been administered in many clinical trials with numerous therapeutic benefits observed. Thus 3-10 g arginine three times each day may be worthy of consideration for treating schizophrenia for the reasons described in this manuscript. Glutamine is the most abundant amino acid in the body. To date glutamine studies have
mostly focused on treating severely burned patients, those experiencing cancer cachexia, or undergoing chemotherapy.63 Therapeutic benefits were observed for all of these situations. The most effective doses were seen after administration of 10-15 g three times each day with the biggest responses seen closer to the 45 g per day dosage. Adverse events generally have not observed for either amino acid.64 However, since nothing is known with respect to doses for treating schizophrenia specifically, extra attention should be made to monitoring the response in all cases. In summary, 3-10 g of arginine three times each day, and 10-15 g of glutamine three times each day may additionally provide therapeutic benefit to the schizophrenic.

Conclusion
There does not appear to be any downside to the simultaneous application of supplemental arginine and glutamine in combination with high dose niacin as a potentially beneficial treatment for schizophrenia. There may be additional therapeutic benefit when this pathway is further strengthened towards more NAD biosynthesis, and more sustained vasodilation via additional glutamine and arginine respectively.

Competing Interests
The author declares that he has no competing interests.

References


In Memoriam

Brian Grove Sparkes
1941–2011

Brian Sparkes, PhD, was born in 1941 in Newport, South Wales, UK, and died December 18, 2011 in St. Michael’s Hospital, Toronto. After immigration to Canada in 1951 he completed secondary school in London, Ontario. Earning two degrees from the University of Western Ontario, Brian was awarded a National Cancer Institute Fellowship to study at McGill University and subsequently earned his doctorate at the University of Ottawa, and he was internationally renowned for ground-breaking research on the role of immune failure in burn injury, first at the Defence and Civil Institute of Environmental Medicine (DCIEM, now DRDC Toronto) and later with Swiss scientists at the University of Basel. For this work he received the 1994 Ambroise Paré Award in Augsburg, Germany. His work at DCIEM on the role of a naturally-occurring sleep-inducing peptide took him to Africa to study victims of sleeping sickness.

Brian’s passionate interest in cancer research began even before graduate school, when his work at the Health and Welfare laboratories in Ottawa led to the first isolation of a bacterial growth inhibitor in 1968. A devoted member of the International Society for Orthomolecular Medicine for many years, he increasingly concerned himself with advising individuals of their best orthomolecular and nutritional treatment options. This activity completely occupied his last few “retirement” years, keeping him from his lifelong enjoyment of playing the piano, and regretfully ending with his own death from an aggressive lymphoma. Brian had a particular concern for maltreated dogs, and his deep understanding of nutritional biochemistry sometimes helped cure the diseased pets of his friends as well.

A memorial was held in Toronto, Canada, on March 3; family, friends and colleagues from around the world attended. For a comprehensive obituary honouring Brian and Orthomolecular Medicine please see: http://v1.theglobeandmail.com/servlet/story/LAC.20120126.Obsparkesatl/BDASTory/BDADeaths.

From a Tribute by Steven Carter at the Memorial:

Brian attended the Orthomolecular Medicine Today Conference for the first time in 2001 in Toronto, and every year after that—in Vancouver, Montreal, Ottawa—he was always there, in the front row, keen to learn, asking tough questions, always among the small group around the speakers following their talks. He was intent on getting new insights to help him with helping others, to tease out the subtleties of treatment for a person (or pet) he was working with.

Brian was noticed and relied upon by many conference delegates for his solid scientific grasp of orthomolecular medical concepts and practices, and for his inquisitive, searching and open mind. A dedicated enthusiast and passionate advocate of taking responsibility for your health and using diet and supplements as a first line in prevention and treatment, Brian seemed always to be on a mission, working on a case. He visited our office two or three times a year for a chat or to pick up a new book.

We also met at classical music concerts, and we shared an admiration for Anton Kuerti and other fine musicians.

Thank you, Brian, for being an exemplary seeker of truth in medicine and a devoted, caring health consultant in the service of others. We’ll miss you in the front row.
Author Responds to Book Review: Hospitals and Health

Dr. Damien Downing’s generally positive review of *Hospitals and Health: Your Orthomolecular Guide to a Shorter, Safer Hospital Stay*, by Dr. Damien Downing (J Orthomol Med, 2011; 26: 189-190)

The following is in response to the book review of *Hospitals and Health: Your Orthomolecular Guide to a Shorter, Safer Hospital Stay*, by Dr. Damien Downing (J Orthomol Med, 2011; 26: 189-190)

Dr. Damien Downing’s generally positive review of *Hospitals and Health* raised some valid criticisms that deserve answer. One question Dr. Downing repeatedly asked was, “Who is this book really for?”

Publishers immediately ask that very question when a book proposal comes their way. The answer can be “no one,” and refusal to publish. In 2008, when Dr. Abram Hoffer wanted to write a history of hospitals, he faced the same problem he faced some fifteen years earlier when he tried to get his book on vitamin C and cancer published. The cancer book, written by Abram at the direct and repeated request of Linus Pauling, was unable to find a publisher even when Dr. Pauling endorsed it, contributed to it, and personally submitted it to various publishers. It was repeatedly turned down. The book eventually was published in 2000 as *Vitamin C and Cancer*, by Quarry Press, a small but significant firm in Kingston, Ontario. In 2004, it was reissued by the Canadian College of Naturopathic Medicine Press as *Healing Cancer: Complementary Vitamin & Drug Treatments*. The College also published a professional edition in 2011. Persistence paid off.

A history of hospitals was even harder to get published. When Abram and I first discussed this idea, we had already been working with a much larger publisher, Basic Health Publications in California, updating and expanding his famous 1988 textbook, *Orthomolecular Medicine for Physicians*. This time, the agreed target audience was the general public. Accordingly, the book was released as *Orthomolecular Medicine for Everyone* in 2008. That same publisher also released Abram’s and my book *The Vitamin Cure for Alcoholism* in 2009, just a couple of weeks before Abram died. Abram’s very last email to me was that he was telling colleagues about it.

Hospitals and Health is, indeed, part history and part self-help. The book presents both background and solutions to a severe and ever-increasing iatrogenic problem that might more accurately be expressed as “Hospitals or Health.”

Dr. Downing opines that the publisher seems to have “mis-targeted the audience.” He would prefer that the book, “if the aim were to preach to the converted, like me, should be more fact-crammed, but if it were to help prospective patients to reframe their approach to doctors and hospitals - as the cover indicates - I think it should be much shorter and punchier, and perhaps even more anecdotal.” Perhaps so, or, perhaps the public is ready for more than short and punchy. Why not go for it? Popular-press publishing speaks to a big audience. For example, in the three years since its publication, Abram’s revised *Orthomolecular Medicine for Everyone* has gone through many printings and is about to be published in Chinese. Just as Dr. Hugh Riordan wanted “to make orthomolecular a household word,” so did we. The way to do that is to take your message directly to the people, every chance you get.

Having taught school and university students for many years, it is my contention that teaching the public requires first reaching the public. Get the information out there, make it interesting, and make it practical. And while you are at it, teach them more about orthomolecular than they expected. I make no apologies whatsoever for this pedagogical approach. The general reader needs to know that hospitals are genuinely dangerous while genuinely necessary; how it came to be that way; and what s/he personally can do about it now. No, Hospitals and Health is not for physicians. This book is for the people on the other end of the stethoscope.

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If you were a general and had a desperate battle to win, you would send in the best troops you had, even though you knew for certain that many would die. If winning that battle is essential for national survival, those individual deaths would be a price acceptable for the country as a whole. But that particular population-benefiting choice is bad for the combat soldier that stops a bullet. What is best for the population is not necessarily best for the individual. To assume otherwise is the ecological fallacy: the incorrect idea that all that favours the population is also good for the individual. Sometimes altruism is essential, whether it is an animal making a futile attempt defending her young against an overpoweringly strong predator, or soldier throwing himself on a grenade to save his platoon. What has overall statistical validity for a group can result in personal death. Statistics might be right for the bean-counter but they can be very wrong for grandma. I am not a physician and I am not a researcher, and heaven knows I am not a statistician. However, as an ethologist (animal behaviour biologist), this makes sense to me whether I like it or not. Evidence-based medicine does not make sense, even though it sounds right: let’s get the “best evidence” and draw our conclusions from huge studies.

Summarizing Tarnished Gold: The Sickness of Evidence-based Medicine boils down to this:

1. The meaning of “best evidence” is selective data which introduces bias. That is bad science. Any college freshman knows that.
2. EBM misapplies statistics in accordance with the ecological fallacy. This is not trivial: it is a major statistical error.
3. EBM has little, if anything, of importance to say to individuals making rational decisions as to whether or not an individual should use a particular therapy. Misapplied results produce inappropriate conclusions and erroneous actions.
4. EBM is unscientific, irrational, and unethical. Or, if you prefer in everyday language, just plain silly.

When you recover from this, remember who this book’s authors are. Steve Hickey and Hilary Roberts, who brought us politically incorrect but scientifically precise books such as Ridiculous Dietary Allowance; Cancer: Nutrition and Survival; and The Vitamin Cure for Heat Disease, are at it again. Their new book utterly takes the wind out of the sails of evidence based medicine, the latest fad of pharmaceutical medicine. I confess to being biased, as I have myself co-authored two books with Dr. Hickey. But most influential of all, to me, has been my experience working in association with Dr. Abram Hoffer, who unequivocally stated:

“One would be very polite to even describe EBM as pseudoscientific. The word “science” cannot be used anywhere close to what is happening with EBM. It has become the main weapon to prevent innovation. It must be sent back to its archaic roots. Instead, we once more have to learn to think rather than calculate. Double blinds are for the birds. I have been opposed to double-blinds for decades, even though my colleagues and I were the first psychiatrists to do them, starting in 1952. I consider them a license to kill. They are a dangerous fashion. There is no evidence that anecdotal information is any less accurate than clinical information. Where are the good old days, when honest physicians honestly reported what they saw in language that any doctor could understand?” (Saul AW: An interview with Abram Hoffer. J Orthomol Med, 2009; 24: 122-129).

Tarnished Gold: The Sickness of Evidence-Based Medicine is especially well done, and greatly needed. Look around you: people are sick and medical costs are through the roof. How should we, and can we, fix a system like this? What treatments work best? How do we know? There have been so many conflict-
Every time I come across new criticism of the Gerson therapy, I also seem to notice a new book by Charlotte Gerson. She, in defiance of geriatric tradition, as so ably flouted by Linus Pauling and Abram Hoffer, continues to write and publish as she actively and healthfully approaches age 90.

The Gerson therapy was orthomolecular before the word had even been coined. Supplements were virtually unavailable in the 1920s and 1930s. As for centuries, fresh food was the original orthomolecular program. Dr. Max Gerson famously added vegetable juices, and infamously added body-temperature coffee enemas. Juices, he believed, flood the body with nutrients, and enemas quickly rid the body of toxins. Conventional medicine is flatly opposed to the second idea, and not exactly trumpeting the first.

So brace yourself: there is an enema chapter in *Defeating Arthritis, Bone and Joint Diseases*. The idea that these are systemic problems did not originate with Dr. Gerson, but establishing a specific, systemic therapy probably did. The Gerson program can literally be summarized in a single page, and is, in the table on page 138. If you are already interested in the Gerson program, it is likely you have already read a good deal of the content of this current volume. If not, this book is a stand-alone, comprehensive introduction. And as such, it can be an annoying wake-up call. The Gerson program requires change and effort. The prescribed daily thirteen glasses of fresh juice include citrus (once) and what might politely be called a thoroughly generous intake of carrot, green and carrot-apple juices. This perceived glycemnic challenge may be tempered with the fact that the juices are consumed a glass or two at a time, ten times all throughout the day. Labour intensive to be sure: the juice must be freshly made... and on top of that, you actually have to drink it.

But there are compelling reasons to do so. There are over 100 different types of arthritis, painfully affecting tens of millions of people. *Defeating Arthritis, Bone and Joint Diseases* has, in addition to osteoarthritis and rheumatoid arthritis, sections on scleroderma, various forms of lupus, fibromyalgia, myelofibrosis, mixed collagen diseases, ankylosing spondylitis, and gout. The author notes that osteoporosis is high in countries with high calcium intake, particularly if that calcium comes from dairy foods. Dairy products are forbidden on the Gerson program. Abram Hoffer completely avoided milk products. Dr. Hoffer was a supporter of the Gerson program, and interestingly, the Gerson program recommends taking 15 times the US RDA of niacin (but not niacinamide). As Dr. William Kaufman so successfully treated osteoarthritis with niacinamide, this qualifica-
girl who reached her hand into her stocking: “It strikes me that there is something in it.” The same may fairly be said about this book.

- Andrew W. Saul
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The 2nd Congress explores the latest advances in supplementation of nutrition as well as practical information on how to apply the information to patients and create a good preventive, integrative medicine environment. The congress is intended for physicians, biochemists, pharmacists and nutritionists who are interested in learning about this aspect of medicine and correctly applying appropriate treatments.

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The Shute brothers were inducted into the Orthomolecular Medicine Hall of Fame in its inaugural year in 2004 for their trailblazing work in vitamin E. The following letter outlines the Shute legacy and why this gift was made to the ISF.

Dear Mr. Steven Carter, Executive Director, ISF

It was in 1948 that Evan and Wilfrid Shute opened the Shute Institute in London, Ontario, to pursue their pioneering work with vitamin E in cardiovascular disease. As time went on, their interests expanded to include the application of vitamin E to a number of other health conditions. They became outspoken supporters of the principle of prevention, the interactions and interrelationships of vitamins and other nutrients, and holistic approaches to health and well-being. The not-for-profit clinic they established attracted scores of thousands of patients from many countries over 62 years before closing in 2010. Now, as we close down the Evan Shute Foundation for Medical Research, we very much want the Shute legacy to live on in ways which will both honour and perpetuate the contributions of the Shute brothers to human health.

It is in that spirit and with that intent that we wish to donate all remaining assets of the Shute Foundation to the International Schizophrenia Foundation, as your organization embodies principles and practices that Evan and Wilfrid Shute believed in and practised diligently and in the face of considerable professional opposition during their careers. We, as Directors, are enthusiastic about transferring this legacy (and these funds) to you, and look forward to seeing our contribution reflected in the education of health professionals concerning not only the efficacy of orthomolecular/holistic/preventive health practices but also the value of challenging medical orthodoxy, testing new ideas, and sharing them for the benefit of all.

To that end, and with this bank draft for $500,000, we pass to the International Schizophrenia Foundation and the Canadian Society for Orthomolecular Medicine the torch of the Shute Foundation with every good wish for your continuing success.

Yours sincerely,

James Shute, Wes DeShane, Donald Kilpatrick
Directors

Wes Deshane (l) and James Shute (r) present cheque to Steven Carter on February 29, 2012
Manuscripts submitted for consideration and editorial correspondence should be directed to:

Jonathan E. Prousky, ND, MSc, Editor
Journal of Orthomolecular Medicine,
16 Florence Avenue, Toronto, ON, Canada M2N1E9
editor@orthomed.org

All manuscripts will be subjected to a peer review process once they have been approved by the Editor.

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Editorial style articles (limited to 2,500 words) will be considered. An abstract is not required. Editorials will normally be requested by the editor; however, we will consider unsolicited manuscripts.

Clinician's Letters
Letter from clinicians (limited to 2,000 words) can be requested by the editor or suggested from potential authors with at least ten years of clinical experience as a practicing orthomolecular practitioner. We welcome suggestions from elder orthomolecular practitioners on particular clinical pearls.

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Original research manuscripts will be considered. Such articles are papers that report clinically relevant investigations or observations within the journal's scope of interests. The abstract should be structured (as described in page two of "Instructions to Authors"), the text should not exceed 5,000 words, and there should be approximately 20 to 40 references. Figures and tables are encouraged and should be included where possible; however, data should not be repeated in both a table and a figure and accompanying text need not reiterate the information provided in tables and figures.

Brief Reports
Brief Reports are condensed articles with a focused message. They should include a brief abstract of no more than 200 words, text of no more than 1,500 words, 5-15 references, and two tables or figures.

Case Reports/Series
Case reports provide a summary of a single case or several cases and give a concise review of the literature. Case reports should present unusual aspects of common problems or novel perspectives upon, or solutions to, clinically relevant issues. They should include a brief abstract of no more than 200 words, text of no more than 3,000 words, and there should be approximately 10-30 references. For further advice on writing detailed case reports, please refer to Aronson JK: Anecdotes as evidence. BMJ, 2003;326:1346.

Synthesis Papers
We welcome articles of an academic nature that are educational to the orthomolecular community. We also welcome articles that may be hypothesis generating and may create dialogue within the readership. They should include a brief abstract of no more than 200 words, text of no more than 3,000 words, and there should be approximately 10-30 references.

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Review papers provide a synthesis of topics related to clinical aspects of orthomolecular medicine. The text should not exceed 5,000 words and have an abstract that does not exceed 200 words. Review papers can be written as focused systematic reviews or more broadly as narrative reviews.

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