3 Orthomolecular Parenteral Nutrition Therapy

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INTRODUCTION

Nutritional treatments by parenteral route can be considered as valuable tools in the integrative management when added to a conventional treatment set, both in acute and chronic diseases.

Its main objective is to recover quickly and regain stability in the internal environment (biological terrain). They are also directed to ensure the proper management of homeodynamic (Lloyd et al. 2001) mechanisms, and to maintain or recover the molecular chemical conditions that guarantee health. Their role is crucial in chronic degenerative diseases, which often oral supplementation of therapeutic nutrients does not elicit a proper response. One of the main limitations for the successful use of the oral route is the abnormal function of the gastrointestinal mucous membranes from toxic and proinflammatory dietary habits (Taira et al. 2015, Woting and Blaut 2016, Li et al. 2016). Along with the resulting disturbances of the microbiota, this usually causes abnormalities in the intestinal permeability and a compromised capacity in the absorption of nutrients, radically interfering factors involved in the absorption and utilization of nutrients.

During the last 30 years, orthomolecular nutrition has been developing a path in integrative medicine, based on the crucial role of basic nutrients in:

- The recovery of chronically ill patients,
- The optimization of therapeutic responses to conventional treatments,
- The strengthening of homeodynamic mechanisms (through the psycho-neuro-immuno-endocrine links).

All these possibilities allow the patients to return to normal daily life in a more physiological way, since many of the delays in the recovery processes are due to nutritional imbalances. Unfortunately, the lack of knowledge of many conventional colleagues regarding the therapeutic use of nutrients many times leads to criticism of a method of great value in daily clinical practice.

Nutritional Deficiencies/Insufficiencies that Support Intravenous Supplementation

Nutrition and orthomolecular supplements are optimal aid measures for most medical treatments. A patient recovers easier when the immune, endocrine, and neural systems (as master regulator systems for the rest of the body) are well nourished. On the other hand, the patient with nutritional imbalances will experience more difficulties overcoming the tendency to biological deregulation.

Unfortunately, in the modern world, many circumstances combine to create an increasingly poor state of nutrients, especially because it is not easy to find the right way to ensure the maintenance of health and structural/functional remodeling.

Understanding the concepts of deficiency and insufficiency plays a pivotal role in understanding the importance of intravenous nutritional therapy. This fully justifies the use of this type of orthomolecular practice, when facing serious nutritional issues in many patients. An historical misconception in the therapeutic use of nutrients has been limiting them to the critical patient, ignoring that for several nutrients, deficiencies/insufficiencies are widespread in the general population.

For some clinical settings, dietary amounts of many nutrients or oral supplementation based on the Recommended Daily Allowance (RDA) can be considered unable to attain clinical responses. In other cases, clinical improvement will take months to appear, thus making intravenous supplementation an interesting method of treatment.

Nutritional foodstuff values' tables of the commonly consumed foods serve only as reference values. Nonetheless, these tables do not reflect necessarily the actual state of the nutrient contents. This has been explained by many factors, for example, the lack or deficiency of a specific nutrient in the soil where these foods have been grown (Joy et al. 2016, Li et al. 2016). There are many other influencing factors, like agrochemical exposure of the crops, environmental toxicity, conservation, manipulation, and transport conditions, refinement of many foods, cooking techniques (peeling, high temperatures, cooking time), and so on, which may significantly impair the nutritional quality of the foods we consume every day (Teixeira et al. 2012, Gemenet et al. 2016, Poblaciones and Rengel 2016). A sustained consumption of nutritionally poor foods, slowly but inexorably leads to nutrient deficiencies among the population.

Some examples of specific nutrient deficiencies in foods/others are

- Preservation and storage processes make vitamins E, C, and/or B1 significantly dwindle its biological potential.
- The consumption of refined grains increases the needs of B complex vitamins and chromium to maintain the glucolipidic balance.
- Inclusion of "fake foods" (artificial flavoring and coloring of foods) compromise the availability of other nutritional factors.

- The little exposure to sunlight promotes global epidemic of hypovitaminosis D.
- Tobacco components (active or passive) affect epithelial barrier and mucosal systems, increasing the need of antioxidants (e.g., vitamins C and E).

Alcohol, a known liver toxin, reduces the absorption and bioavailability of many micronutrients, like vitamin C, vitamin E, B complex vitamins (thiamin, niacin, pyridoxine, folic acid, cyanocobalamin), calcium, magnesium, zinc, vitamin A/carotenoids, and SAMe (Lieber 1990, Ghorbani et al. 2016).

- Modern world stressful way of life increases the requirement of nutrients like glutamic acid, L-glutamine, L-arginine, antioxidants, and/or B complex vitamins.

Significant imbalance of essential fatty acids favors a trend toward persistent low-grade inflammation as a consequence of the distortion from modern habits and our Paleolithic genome (Ruiz-Núñez et al. 2016).

- Drug interactions with nutrients can affect their metabolism. This can be seen especially in polypharmacy patients due to chronic and/or multiple diseases. In some cases, specific medications alter the dynamics of the gastrointestinal system, affecting the absorption of nutrients (e.g., azathioprine, many of the chemotherapeutics, antibiotic related diarrhea, etc.).

Processing, storing, and heating/cooling of food may cause a loss of 40% of vitamin A, 100% of vitamin C, 80% B complex vitamins, and 55% of vitamin E (Harris and Karmas 1975).

Cutting or crushing food during preparation of meals starts enzymatic oxidation reactions that destroy important nutrients. The average loss of minerals and other nutrients from vegetables can reach more than 30% (Saxena et al. 2009).

All these factors lead us to understand that there is a considerable possibility of requiring parenteral nutritional replacement in patients with chronic or degenerative diseases. In this particular situation, the orthomolecular treatment has to ensure a quick and effective recovery of the deficient/insufficient nutritional components. There are other contexts like the acute patient. In that case, some of the nutritional circumstances may be similar, but the intravenous supplementation regimes are usually used for short periods of time. After the cause of the acute problem has been detected and corrected, it can be expected that any resulting nutritional deficiency does not prolong after a supplementation period limited in time.

Injectable Solutions in the Clinical Practice

As in any other pharmaceutical specialty, orthomolecular medicine requires the knowledge of the respective methodology of preparation of the nutritional therapeutic solutions to prevent any avoidable risk for the patient. When prepared under the proper manufacturing conditions, the orthomolecular intravenous solutions can be applied safely by trained personnel (both in the outpatient and in the inpatient setting).

The supplements suitable for nutritional therapy should have either pharmaceutical grade or should be manufactured by specialty compound pharmacies with experience in the preparation of injectable medications (Remington 1995). On the other hand, the attending physician practicing parenteral nutrition therapy should know the legislation and regulatory issues according to the country of practice. This must be taken into account especially for those regulations pertaining to the use of parenteral solutions in patients.

There are some fundamental conditions that the nutritional solutions should fulfill. All injectable nutritional/functional supplements must be sterile, pyrogen-free, and meet the stability and physicochemical conditions to assure the medical objective sought with this methodology treatment, while avoiding any complication arising from manufacturing issues (Lawrence 2007).

The use of the injectable route for orthomolecular supplementation becomes even more important in some specific situations related to the patient's condition:

- When the oral route is not possible, or when the conditions of the gastrointestinal tract do not guarantee the proper absorption of nutrients (from widespread intestinal dysbiosis to precise pathologies like short intestine syndrome);
- When the chemical nature or characteristics of the drug impede a satisfactory absorption by the oral route (e.g., Glutathione);
- When a quick correction fluid or circulating electrolytes is needed, or when a particular nutritional correction is mandatory (e.g., hypokalemia);
- When a faster therapeutic effect is required, due to the clinical condition or urgency;
- When the attending physician prefers direct control over the components and dosage of a nutritional mixture, according to the therapeutic objective.

Similarly, one might consider some specific situations in which the parenteral route can be recognized as the best way to ensure safety in the patient's treatment:

- When the pharmacological/clinical effect needs to be guaranteed, since the plasmatic levels obtained by the intravenous route do not depend on the process of intestinal absorption;
- When the treatment schedule must be correctly complied within the scope of inpatient institutions, as well as home care services;
- When the osmolarity, pH, or tonicity of the supplements are factors to be considered in the context of the patient (e.g., renal, cardiac, or hepatic disorders).

It is important that the health professional is trained specifically in the methodology of orthomolecular parenteral therapy. That allows a correct diagnosis of a particular medical condition, a determination of the type of orthomolecular treatment. It also allows the suitable preparation and administration of injectable components, as well as the recognition and prevention of any possible complications. Although not commonly seen in routine practice, some examples of these are: phlebitis, thrombosis, tissue damage, stroke, and local or systemic infection. As in any injectable therapy, when mistakes in dosage, volumes, and combinations are avoided, the risk of complications is clearly decreased.

The orthomolecular parenteral therapy comprises both intravenous and intramuscular administration. The best pharmaceutical presentations for these therapeutic routes available in the market are

- Ready to use pharmaceutical aqueous solutions,
- Dry soluble products with specific solvents, and/or
- Concentrated pharmaceutical solutions, which can be diluted prior to their use.

Application Routes in Parenteral Nutrition

Aqueous solutions are employed for the intravenous application. A peripheral vein (in most cases from the upper limbs) is chosen and varying volumes ranging from 0.5 to 1000 mL are dripped intravenously.

In some cases, there is also the possibility to apply "boluses" with volumes up to 10 mL. In other cases, intermittent solution applications can be performed over time (e.g., once a week), with volumes ranging from 100 to 500 mL. If total infusion volume exceeds 1000 mL or in some specific contexts like chelation therapy, it is recommended to have an infusion pump to perform a more controlled drip.

As it was mentioned before, the intravenous route has the advantage of not depending on the enteral absorption since the orthomolecular mixture is injected directly into the bloodstream and

from there to the interstitial compartment and to the cell. It must be taken into account that this is a faster route with more rapid clinical effects, but one should also be aware of possible dangers associated to this same reason. Adverse reactions may be related to:

- Inappropriate use of supplements (e.g., an excess of intravenous L-tryptophan or Zinc could cause headache in sensitive patients);
- Empirical or random combinations (e.g., including unbalanced proportions of antagonistic nutrients as copper/zinc or L-lysine/L-arginine in the same solution or mixes of multiple minerals with ascorbic acid);
- Negligence in preparing the mixture;
- Not considering physical parameters of the solutions, such as tonicity or pH.

All these previous factors can be clearly associated with the lack of knowledge regarding the proper methods of orthomolecular parenteral nutrition. In that sense, they can be prevented easily if simple measures are taken.

Nonetheless, there are some other plausible undesired effects related to idiosyncratic reactions, sometimes not adverted by the patient though his or her life. Some people can have individual sensitivity to any orthomolecular component, although some of them have produced this type of reaction more frequently than others (e.g., iodum, thiamine).

In their original presentation, most orthomolecular injectable solutions are hypertonic. If used in this form, they could generate hemolysis (Olszewer and Teruya 2009). Prior to the intravenous application, hypertonic presentations must be diluted in suitable physiological solutions, optimizing osmolarity. The final solution should be isotonic or slightly hypotonic, to be adequately tolerated by erythrocytes (Botella Dorta 2004).

Regarding the pH parameter, neutral solutions between pH 6 and 7.5 are recommended. It is important to mention that blood has a significant buffering capacity, mainly concerning acids.

The intramuscular route can also be considered for the supplementation of orthomolecular nutrients. In that case, liquid medications in aqueous solutions or aqueous/oily suspensions are preferred, with volumes ranging from 1 to 5 mL. For these applications, gluteal or deltoid muscles are ideal. Their striated muscle nature endows them with wide vascularity and few sensory innervations, allowing a better absorption accompanied with low pain (Botella Dorta 2011).

Intramuscular injection allows differential absorption times, depending on the nature of the applied solution. For aqueous solutions, rapid absorption will be seen, while oily solutions/suspensions can be considered a deposit form with slow absorption rates. The proportion between oil and water in these solutions will determine its absorption rate.

When the pH of intramuscularly injected products is close to the plasmatic one, the application shall be less painful. In another way, when the pH is too acidic or alkaline, this can generate secondary reactions. In most cases there could be a simple congestion, but in extreme cases there can be an inflammatory process and even tissue necrosis could occur (Lawrence 2007). A slight hypertonic solution could be more easily absorbed.

Some adverse reactions with intramuscular injection are related to the nature of the drug itself. It is widely known how vitamin B1 and B complex vitamins produce much more pain when injected through this route. This fact can be reduced in some degree when these types of orthomoleculars are injected deeply into the gluteal muscle.

Preparation of Mixtures for Parenteral Nutrition

Due to the practical importance of this aspect, it will be also mentioned in this chapter.

Health professionals, who include orthomolecular parenteral nutrition among their practices, should be trained particularly in the preparation of nutrient mixtures. The development of an institutional "procedures manual" is strongly suggested (Sobotka et al. 2009). This type of manual should

include: detailed instructions about all the processes related to the preparation of the mixtures (responsible personnel both for the preparation and application, proper facilities, available supplements, optimal quantities and number of supplements to be used, etc.).

The procedures manual is primarily a safety measure for the patient, the health staff, and the institution. It also plays an important role in the institutional qualification/habilitation processes with the local sanitary authorities granting the permissions required to perform such procedures.

The health personnel involved in parenteral orthomolecular therapy must include one coordinator (usually a registered nurse) skilled to conduct training to the rest of the team. This training should cover the following topics (Botella et al. 2002, World Health Organization 2003, Sobotka et al. 2009):

- Hygiene and aseptic techniques. This point is especially important due to the emergence of parenteral therapy-associated mycobacteriosis;
- Knowledge of possible physical or chemical incompatibilities between prescribed nutrients and/or between nutrients and diluents;
- Potential instability of intravenous mixture or nutrient diluent mixture;
- Hazards or risks of microbiological contamination during intravenous mixture preparation, during the time of peripheral access puncture, or during the mixture application;
- Restrictions on temperature, sunlight exposure, and other storage product requirements. Label-related issues (Kumar et al. 2013), such as passive errors due to lack of attention when reading the labels, poor quality labels (allowing deterioration of important data related to the supplement that makes them difficult to read), or even mislabel itself;
- Human errors like adding the same supplement more than once, or in excessive amounts;
- Lack of knowledge regarding a particular nutrient, particularly in the case of potential adverse reactions or adverse effect during its application.

Special Care in the Preparation of Orthomolecular Mixtures

Incompatibility

Incompatibility can result from physical or chemical interaction between components.

Attention must be called to the presence of physical incompatibility which is visually noticeable. It is characterized by a variety of possibilities as precipitation, clumping, cloudiness, frothiness, or changes in color of the mixture. Any of these abnormalities occurs when there is incompatibility between two or more components. Another option would be the incompatibility between any of the nutrients and the solvent vehicle. The physical changes can be evident in the solution bag even from the time of preparation of the mixture, but also during the application of it (Saldaña–Ambulódegui 2012).

Another potential incompatibility arises from the chemical interaction of orthomolecular mixture components. The possible responses to chemical incompatibilities include an affection of the purported therapeutic action of the supplementation (from partial to complete loss). It could also derive in the eventual augmentation of known potential toxicity of one component, or in the generation of toxic compounds with undesirable effects. The emergence of thrombophlebitis is not common but possible, mostly related to an incorrect management of the parenteral technique. As with any intravenous application, there exists the theoretical chance for developing embolisms, a rare complication not seen in more than 30 years of experience with orthomolecular injectable medications in our practice.

Usual potential factors affecting compatibility or stability of a parenteral nutrition solution are

- Problems with the pH of the mixture, which is considered the most critical factor (Olszewer and Teruya 2009).
  - Regarding the intravenous solutions, the closer the pH value is to 7, the less chance there is of having a painful or risky application. In physiologic conditions, blood has a pH of approximately 7.35, slightly alkaline. With the intramuscular injections, solutions with a pH between 4.4 and 8.5 are considered acceptable.

    - Some components are known because of their very low pH: Thiamine, N-acetylcysteine, L-leucine, or Cyanocobalamin. In turn, there are others like DMSO, which tend to have alkaline pH (around 10).
- The sequence in which the components are added.
- Modifications of components by exposure to light and/or inadequate temperatures (previous or during the application; e.g., alpha lipoic acid, ascorbic acid).
- Difficulties or problems with dilution of any component of the mixture.
- Significant changes secondary to the time elapsed between preparation and application.
- Complications arising from the type of diluent used.
- Improper conditions of packaging, transporting, and storing.

The institutional procedures manual serves as a useful method to minimize the risk of incompatibilities, therefore preserving the integrity of patient care during orthomolecular injectable therapy. There are some specific recommendations to observe in that regard:

- The solutions to be injected must be prepared and then injected in the shortest possible time. Avoiding the preparation of orthomolecular mixtures in advance should be the general rule. The concept of mixture stocking should not have any role in orthomolecular nor in integrative medicine.
- The number of components of a nutritional mixture should be kept to the lowest, and should follow rational protocols established previously, according the therapeutic target(s).
- If the mixture includes components with different pH, a previous check of this pH in their labels is recommended, to mix and add them in descending pH order (from alkalines to acidics).
- There exist several incompatibilities between some injectable orthomoleculars. For example, ascorbic acid plus minerals in the form of sulfate salts, due to the precipitation possibility of the last ones. Incompatible medications should never be mixed. They should be prepared in different solution bags and attention should be paid to the order of intravenous application of these solutions.
- Many practitioners of integrative medicine perform orthomolecular infusions along with other types of therapeutic approaches. When using medications with bio-regulatory properties (antihomotoxics and/or homeopathics) simultaneously during the orthomolecular mixture, the intravenous catheter should be used. Ideally, a washout of the intravenous line with 10 mL of sterile water solution should be performed before and after the injection of the bio-regulatory medication. When using two or more bio-regulatory medications, a minimum of 5 minutes should be left between their application.
- In case of having any doubt, a consult with the pharmacist of the institution is highly recommended.

Instability

Instability of some orthomolecular nutrients arises from chemical reactions considered undesirable and preventable, but in most cases irreversible. These reactions occur either because of mixing incompatible components in the same solution or external influences. The result could be in the form of toxic compounds or as a compromise in the therapeutic effectiveness of the nutrients. The most known of these influences are

- Oxidation of antioxidants after exposure to light and/or heat (especially alpha lipoic acid, but attention must be paid also with ascorbic acid, glutathione (Yamamoto and Ishihara 1994, Fleming 2016), and vitamin B5);

- Destruction by the action of ultraviolet light (B complex vitamins, particularly riboflavin, thiamine, pyridoxine, Cyanocobalamin, and folic acid (www.helapet.co.uk/downloads/lightaffectingdrugs.pdf));
- Hydrolysis of amino acid (polypeptidic) chains can result from their inclusion in acidic solutions.

Sterility and Modifications Due to Contamination

The sterility of an injectable nutritional solution is a mandatory condition. Microbiological controls of injectable drugs must be carefully fulfilled. When handling solution bags, intravenous application equipment, catheters, and so on, sufficient precautions have to be taken care of.

Beyond the required quality of the used materials, contamination can occur during the preparation and/or the application procedure itself. This phenomenon can be related to inadequate staff hygiene when preparing and administrating the solutions, and also to inappropriate infrastructure institutional conditions (Akers and Larrimore 2003, Williams 2005, http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/generalChapterInjections.pdf).

Apyrogenicity

Nutritional products intended for parenteral use must be free of pyrogens. Defensive reactions against a variety of microorganisms (Gram-negative or Gram-positive bacteria, viruses, and fungi), or its endotoxins (lipopolysaccharides, LPS from Gram-negative bacteria) can be found in parenteral pharmaceuticals and medical. Endotoxins are large molecular weight complexes (~106 Da) associated with and expressed in the outer membranes of Gram-negative bacteria (Kluger 1990, Hartung and Wendel 1995, Henderson et al. 1996, Rosimar et al. 2004). This is a reason of concern to the pharmaceutical industry, and as such, all the necessary means to avoid this situation must be present.

In our system, the endotoxin/LPS binds to the specific toll-like receptor 4 (TLR4) complex on the monocyte membrane (Lu et al. 2008) initiating the signaling and transduction inflammatory pathway. This pathway comprises several reactions leading to the induction of endogenous pyrogens such as Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). The endogenous pyrogens then cause a change in the thermoregulation in the hypothalamus toward a higher body temperature in order to optimize all the immune system responses. In the case of exogenous pyrogens, the Interleukin-8 (IL-8) is induced in the monocyte. This chemokine by nature has different functions than the previously mentioned ones.

Pyrogens are hyperthermia inducing substances. They can come from intact, dead, or disintegrated microorganisms, whether they are pathogenic or not. In the case of intact (living) microorganisms, they often result from their metabolic products such as denatured proteins. Gram-negative bacteria are particularly known due to their capacity of pyrogen production. In comparison to other pyrogens, LPS are more resistant to heat (Hartung et al. 2001, Roth and Blatteis 2014) inducing higher febrile reactions. In this context, it is mandatory that the sterilization process is performed with the correct temperatures and controls.

From the clinical point of view, regarding other types of microorganisms, pyrogens from fungi are considered less important since they tend to produce only a slight temperature elevation. As demonstrated in experiments with rabbits, fungal mannans can be considered pyrogens by themselves (Nagase et al. 1984). Its effect is independent from the one of LPS, but has a weaker intensity.

In cases of contaminated orthomolecular therapeutic mixtures administrated intravenously, a febrile reaction occurs. This situation does not have any relationship with the nutritional agents included in the mixture, since none of the usual orthomoleculars is known to induce this type of reaction. This hyperthermical effect can go beyond 40°C (104°F) and have a duration ranging from 4 to 12 hours (Morimoto et al. 1988, Rosimar et al. 2004), if an antithermic measure is not taken. Other clinical features of the reaction against pyrogens include cold or chills, joint or lumbar pain, nausea and/or headache.

SPECIFIC PRODUCTS FOR USE IN ORTHOMOLECULAR INTRAVENOUS NUTRITIONAL THERAPY

Historical Considerations

The use of nutrition with therapeutic purposes has a long history in medicine, but it was only until the mid-twentieth century that the intravenous route was a feasible option. McCormick in Canada (McCormick 1959) was probably the first author to come up with the idea of the intravenous intervention in cancer, which according to his theories would arise from a defective collagen remodeling because of vitamin C deficiency.

During the 1970s, Linus Pauling and Ewan Cameron took back these interesting ideas (Cameron and Pauling 1973, 1974, Cameron et al. 1979). After encouraging clinical observations (Cameron et al. 1975), the group of Cameron later began their clinical research on terminal cancer patients, using high-dose intravenous Vitamin C. In their landmark publications (Cameron and Pauling 1976, 1978) they were able to show improvement in function and life expectancy in this oncologic group of patients. The patients receiving the high-dose vitamin C treatment had a median survival time of 300 days more compared to the non-treated patients (Cameron and Pauling 1978).

These claims were promptly scrutinized by researchers in the Mayo Clinic. They were not able to corroborate Pauling and Cameron's observations (Creagan et al. 1979, Moertel et al. 1985), thus disqualifying the treatment of oncologic disease with high-dose vitamin C. This publication closed the doors for the possibility of integrating vitamin C into conventional oncology treatment for many years.

It has already been clarified (González et al. 2005) that the trials from Pauling and Cameron and the ones from Moertel et al. are clearly different in their methodology. Pauling and Cameron used high-dose vitamin C delivered intravenously and the orally, in patients with moderately advanced disease. The Mayo Clinic trial used high-dose vitamin C delivered *only* orally in patients with severely advanced disease.

Additionally, at that time it was not known that the vitamin C pharmacokinetics differ clearly in the parenteral versus the oral use (Padayatty et al. 2004), rendering the studies by Cameron and Moertel incomparable. Prior observations of high-dose vitamin C researchers had already suggested such an effect, since the tumoral regression was possible only when the dose was maintained high enough (Cameron et al. 1975). Cameron did not have the pharmacokinetic data but emphasized the need of a continuous administration of high-dose vitamin C to achieve the expected results (Cameron 1991).

The following decades were characterized by the opposition of the two points of view. High-dose vitamin C advocates continued treating their patients with this approach, and conventional oncology continued rejecting this therapy. Hugh Riordan, MD in Wichita, Kansas contributed building a strong base of work from the practical therapeutic activity in complementary oncology. Dr. Riordan and his team have treated more than 40,000 cancer patients and have published research (Mikirova et al. 2008, 2016a,b, Riordan et al. 2005, Duconge et al. 2007, Padayatty et al. 2006) showing effectiveness for some cancers. The Riordan intravenous vitamin C (IVC) protocol for patients with oncologic disease (Riordan et al. 2003) involves the slow infusion of vitamin C at doses of 0.1–1.0 grams (g) of ascorbate per kilogram (kg) of body weight.

During the 1960s and the 1970s, John Myers, MD, an internist from Johns Hopkins Hospital in Baltimore, made particular remarks regarding the limitation of the oral route to provide an optimal nutrient intake (with therapeutic purposes). He concluded that since the average western world patient has a compromised capacity to absorb nutrients due to the lack of an optimal function of the digestive mucous membranes, the use of intravenous supplementation would be fully justified. Besides the absorptive limitation, there is also the inherent activity of detoxification systems (i.e., the "1st-pass effect"), turning the oral route into a suboptimal one. Hence, only a small fraction of the vitamins and minerals ingested by the average patient (either in food or in pills) are actually being successfully absorbed and then lead into the bloodstream. Dr. Myers started using a safe

mixture of key nutritional supplements which were administered in a single intravenous infusion (directly providing these nutrients to each cell in the body).

Although the pioneering work of Dr. Myers has always been recognized in the orthomolecular medical community, the exact composition of the so-called "Myers' cocktail" was not precisely known. The information related to Myers' patients was incomplete and there weren't any official publications available about this orthomolecular treatment, beyond anecdotic material. According to the review made by Dr. Alan R. Gaby, MD (Gaby 2002) who took over Dr. Myers' practice in Baltimore after his passing, it seems that Myers used a 10-mL syringe to administer a combination of magnesium chloride, calcium gluconate, thiamine, pyridoxine, cyanocobalamin, calcium pantothenate, and vitamin C. The exact amounts of the individual components were unknown, but Myers apparently used a 2% solution of magnesium chloride, rather than the more widely available preparations containing 20% magnesium chloride or 50% magnesium sulfate.

Based on the alleged "Myers' cocktail" composition by Gaby, he administered such a mixture of magnesium, calcium, B complex vitamins, and vitamin C. This author along with a group of collaborators report (Ali et al. 2009) satisfactory clinical results in patients with migraine, fatigue (including chronic fatigue syndrome), fibromyalgia, acute muscle spasm, upper respiratory tract infections, chronic sinusitis, seasonal allergic rhinitis, acute asthma attacks, and other disorders. According to these authors, through the years they have administered more than 1500 Myers' cocktails to patients with various clinical conditions.

Other orthomolecular nutrients like Glutathione have also been reported to be useful when administered together with Myers' cocktail, particularly in the context of cardiovascular disease (Forman et al. 2009).

According to our experience, since 1975 in the Academia de Medicina Biológica de Los Robles (Los Robles Biological Medicine Academy) in Popayan, Colombia, Dr. Germán Duque, MD initiated the intravenous administration of the so-called Moros' mineral constellations. This combination of oligo and macroelements was developed by Dr. Gustavo Moros, a Venezuelan cardiologist some years before. Dr. Moros used fixed doses of various minerals in different salt forms. This supplementation allows the complete reposition of the relative circulating pool from the most important minerals, providing a basic nutritional load for the extracellular matrix and subsequently for the cells. This type of intravenous orthomolecular compound has been the basis of the parenteral nutritional approach in our clinic for the last 35 years. There are several commercial presentations available in South America, for example, MM–16 Forte (18 minerals) from HeilPro DKN® (Cali, Colombia), MinTraz (19 minerals) from OrthomoLab® (Cali, Colombia), and Nutri-MINS (16 minerals) from BioMolec® (Quito, Ecuador). All these multimineral compounds conserve the Moros' concept of including a myriad of mineral salts as the nutritional orthomolecular supplementation method in both chronic and acute patients.

Theoretical Basis for the Therapeutic use of Intravenous (IV) Nutrients

Therapeutic intravenous administration of nutrients has some advantages over other routes, and of course like any therapeutic measure, is not free of some disadvantages.

Regarding the advantages, this route can achieve serum concentrations which are not obtainable with oral or even intramuscular (IM) administration.

For example, as the oral dose of vitamin C is increased progressively, the serum concentration of ascorbate tends to approach an upper limit, because of both saturation of gastrointestinal absorption and a sharp increase in renal clearance of the vitamin (Blanchard et al. 1997).

When the daily intake of vitamin C is increased by 12-fold, from 200 mg/day to 2500 mg/day, the plasma concentration increases by only 25% (from 1.2 to 1.5 mg/dL). The highest serum vitamin C level reported after oral administration of pharmacological doses of ascorbate is 9.3 mg/dL (Harakeh et al. 1990). In contrast, the IV administration of 50 g/day of vitamin C resulted in a mean peak plasma level of 80 mg/dL (about 12 times higher).

Similarly, oral supplementation with magnesium results in little or no change in serum magnesium concentrations, whereas its IV administration can double or triple the serum magnesium levels (Okayama et al. 1987, Sydow et al. 1993).

Many nutrients have been shown to exert pharmacological effects, which are in many cases dependent on the concentration of the nutrient (so as in most medicinal substances).

For example, an antiviral effect of vitamin C has been demonstrated at a concentration of 10–15 mg/dL, a level achievable with IV but not oral therapy. In another context, at a concentration of 88 mg/dL in vitro, vitamin C was able to destroy 72% of the histamine present in the medium (Uchida et al. 1989).

Lower concentrations were not tested, but it is possible that serum levels of vitamin C attainable by giving several grams in an IV push would produce an antihistaminic effect in vivo. Such an effect would have implications for the treatment of various allergic conditions.

Magnesium ions promote relaxation of both vascular (Iseri and French 1984) and bronchial (Brunner et al. 1985) smooth muscles, specifically with higher doses. This effect might be useful in the acute treatment of vasospastic angina and bronchial asthma, respectively.

These are only a couple of examples, but it is likely that these and other nutrients exert additional pharmacological effects (currently unidentified) when used in high concentrations.

In addition to having direct pharmacological effects, IV nutrient therapy may be more effective than oral or IM treatment for the correction of intracellular nutritional deficits. Some nutrients are present at much higher concentrations in the cells than in the serum. For example, the average magnesium concentration in myocardial cells is 10 times higher than the extracellular concentration (Frustaci et al. 1987).

This ratio is maintained in healthy cells by an active-transport system that continually pumps magnesium ions into cells against the concentration gradient. In certain disease states, the capacity of membrane pumps to maintain normal concentration gradients may be compromised. In one study, the mean myocardial magnesium concentration was 65% lower in patients with cardiomyopathy than in healthy controls (Frustaci et al. 1987), implying a reduction in the intracellular-to-extracellular ratio to less than 4-to-1. Considering that magnesium plays a key role in mitochondrial energy production, intracellular magnesium deficiency may exacerbate heart failure and lead to a vicious cycle of further intracellular magnesium loss and more severe heart failure with potentially disastrous consequences.

Intravenous administration of magnesium, by producing a marked, though transient, increase in the serum concentration, provides an opportunity for ailing cells to take up magnesium against a smaller concentration gradient. Since these cells belong to a pathological context, the nutrients taken up by them after an IV orthomolecular infusion may eventually leak out again. Nonetheless there is always the aim of inducing repair and healing phases from the replenishment of nutrients, even before the leak out happens again. With time, if cells are repeatedly "flooded" with nutrients, this improvement may be cumulative.

In the author's clinical observation, some patients who receive a series of orthomolecular IV injections become progressively healthier, not only from their main cause of consultation, but also from other minor complaints in their clinical history. In these patients, the interval between treatments can be gradually increased, and eventually the injections might be no longer necessary.

This can be considered as one of the disadvantages of the IV route, since not all the patients are willing to receive injections. Of course, this is not limited to orthomoleculars, but extends to any injectable product/medication.

Other patients require regular injections for an indefinite period of time in order to control their medical problems. This prolonged necessity of orthomolecular IV injections could conceivably result from any of the following:

1. Chronic disease states which are hardly reversible (e.g., many oncologic patients).
2. Advanced age, since it is characterized among others by a difficulty in the normal intestinal absorption of nutrients and the secondary deficits.

A genetically determined impairment in the capacity to maintain normal intracellular concentrations of a specific nutrient (Henrotte 1980).

An inborn error of metabolism that can be controlled only by maintaining a higher than normal concentration of a particular nutrient (Camp et al. 2013).

3. A persistent renal leak of a nutrient (Booth and Johanson 1974) or several nutrients, like in CKD (Merrill 1956).

Potential Side Effects Considerations

It is important to mention that the use of IV vitamin C must take into account a genetic defect called "Glucose-6-Phosphate Dehydrogenase Deficiency," or G6PD-deficiency, also known as "favism." This is a genetic mutation found in people of African or Mediterranean origin. If a patient with favism receives IV vitamin C, it can result in hemolysis (destruction of red blood cells, RBCs). This happens because without this critical enzyme, the RBC is not able to recycle Glutathione and thus is not able to handle oxidative stress/damage. Without Glutathione to protect it, the RBC will be destroyed, leading to anemia. This is a potentially very dangerous situation since it can end up in acute renal failure, and can even be fatal (although this is rare).

A genetic screening for G6PD-deficiency in patients programmed to receive IV vitamin C is thoroughly recommended. The practice of medicine and of orthomolecular supplementation is shaped by socioeconomical status. In that sense, we are aware of the screening being performed regularly in developed countries. On the other hand, in our experience in third world countries, where the test is expensive or simply not available, it is possible to begin IV vitamin C with low doses (e.g., 3–5 g) and tell the patient to pay attention to any change in the color of the first urination after the infusion. If there has been any low-level hemolysis (as evidenced by rose or light red color in the urine), the genetic test is indicated.

Although this genetic defect has been reported in the literature as a high incidence one (Minareci et al. 2006), in our particular Latin-American population we have not been able to see the first case in more than 30 years using low, medium, and high doses of IV vitamin C.

In any case, most patients with this mutation are already aware of their condition (given they were born with it) and the likelihood of red cell hemolysis/destruction with the ingestion of certain common foods, such as beans (especially fava beans). Any family history of favism reported by the patient obligates to the appropriate test before receiving IV vitamin C.

Another special group to consider is the chronic renal insufficiency (CKD) patient. In this case, some nutrients included in the orthomolecular infusions represent an increased risk of accumulation. This is due to the compromise in the blood filtering function of the kidneys, which helps maintain normal levels of fluid and ions in the bloodstream. If this process is impaired, receiving certain amounts of IV fluids possess an increased risk of "fluid overload" state. This applies also for patients with congestive heart failure and/or atrial fibrillation. Special precaution must be observed in patients taking Digoxin or other potassium-depleting drugs (e.g., some diuretics), since potential electrolyte imbalances in this group of patients can lead to heart arrhythmias in an easier way in comparison to the general population.

In any of these conditions, IV nutrients can be used but there are special cautions with volumes and duration of the infusions, to avoid a "fluid overload" state. Additionally, CKD can also impair the ability to filter and/or reabsorb specific minerals. Certain ions (K^+, Mg^+, Ca^{4+}) or mixes of them, with a higher osmolality, could eventually lead to accumulation of them and potential toxicity.

Intravenous magnesium is known to affect blood pressure (BP) and potentially lower its records. Magnesium influence in blood pressure is evident when it is used daily in hospitals around the world (particularly in the management of pregnancy-induced hypertension, or "toxemia gravidarum"). Patients with low blood pressure are advised to report any symptoms related to such conditions during and/or after an orthomolecular IV treatment. This phenomenon is usually counteracted

with the total volume of the infusion, but it could persist if the tendency to hypotension is notorious and/or if the dose of magnesium is high. Thus, caution is recommended in patients with low BP.

A similar caution must be mentioned in patients with tendency to hypoglycemia. Some orthomolecular nutrients have the capacity to influence the carbohydrate metabolism, such as chromium, zinc, manganese, vanadium, some B complex vitamins, among others (Sárközy et al. 2014). Glucose can bind to DMSO and be carried into cells. All these potential influences can lead to lower blood sugar levels. Patients with hypoglycemic tendencies are advised to report any symptom related to such condition during and/or after an orthomolecular IV treatment. In our institution, there is the universal recommendation of ingesting at least some food before any IV orthomolecular infusion.

Allergy is also a theoretical reason for concern, although the rarest of the potentially adverse reactions to occur. There is always of course the possibility of a patient with an unknown allergy. In that case, individual patients may have an allergy to a component of the IV combination and this can evoke an allergic response. Given the simple molecular characteristics of most of the orthomolecular nutrients used in IV infusions, it is not likely that an allergic reaction presents. Nonetheless, there are specific concerns about iodine, which in fact is recognized in medicine as a potentially strong allergen for some individuals. If there is any suspicion of a potential allergic sensitivity, the suspected substance should be avoided in the orthomolecular mixture. In the very infrequent case of an allergic reaction, the respective control treatment should be commenced quickly.

Intravenous (IV) Orthomolecular Therapeutic Agents

A wide range of substances that are part of the nutritional orthomolecular therapeutic approach can be injected through the veins into the bloodstream. Each nutrient has specific medical objectives, but since habitually a single nutrient is involved in several metabolic pathways and exerts actions in several tissues, it is common that the list of objectives/functions can rise to 5 or 6 per nutrient. When injected in conjunction with other nutrients with the same objective, a synergistic action can be expected, but this is more a theoretical concept given the difficulty to measure it. The nutrients in orthomolecular medicine can be grouped in several categories according either to their action or to their chemical structure. The most common ones will be reviewed in the next section of the chapter.

Antioxidant Agents

Vitamin C (Ascorbic Acid)

It is important to mention that vitamin C can act as an antioxidant or as a prooxidant depending on a variety of factors, like the dose administered and the physiologic or pathologic state of the recipient (Levine et al. 2011, Chakraborthy et al. 2014). Historically, lower doses up to 5 g have been considered as antioxidants (Traber and Stevens 2011), while the higher doses from 15 g and above have been recognized as prooxidant (Chen et al. 2008, Mendes-da-Silva 2014). Although this concept can prevail most of the time, there have also been publications (Hininger et al. 2005) which challenge this postulate. Of course, oxidative stress is a complex phenomenon to study and drawing conclusions only from basic studies can not necessarily be applied to the clinical reality. In the clinical and therapeutic contexts (where type III complexity is the rule rather than the exception and thus they are better understood with a systems biology approach (Welsby 1999)) the dose concept cannot be static, as in the case for the use of IV vitamin C.

Different studies have been published suggesting beneficial results in many clinical situations. One of the most prominent fields for the use of IV vitamin C is the modulation of the tissues, resulting in an aid to the healing process. This has been observed, for example, in a postsurgical setting, where the supraphysiologic supplementation of ascorbic acid resulted in improvements of the anastomosis healing. The authors attributed the effect to a better control of the local inflammatory process, and to a better quality and quantity of the collagen produced locally, resulting in a higher strength of the anastomosis (Cevikel et al. 2008).

Another possibility for the orthomolecular use of IV vitamin C is in the oncology field. In the clinical setting, doses of 10–75 g of vitamin C administered intravenously exhibited a cytotoxic effect upon entering cancer cells. According to their interesting results, the research team affiliated with the Bezmialem Vakif University Medical Faculty in Turkey encourages the use of IV vitamin C along with radiotherapy for the treatment of patients with bone metastases (Kiziltan et al. 2014).

The besought mechanism of action for the antitumoral effect of high dose IV vitamin C is the augmentation of hydrogen peroxide at the extracellular level (Riordan et al. 1995). Since the tumoral cells lack the proper antioxidative defenses (catalases, among others), they perish from the exposure to these type of doses (prooxidant) (Chen et al. 2007, Park 2013).

There are other possible additional mechanisms of action supporting the use of high dose IV vitamin C in cancer patients. In a basic study (Yeom et al. 2009) Korean authors found that the carcinostatic effect induced by high dose concentrations of ascorbic acid occurred through the inhibition of angiogenesis, according to several parameters of tumor evaluation (biopsy results, gene expression studies, and wound healing analysis, both in vivo and in vitro).

Several treatment protocols have been reported for high dose IV vitamin C as a therapeutic tool in patients with cancer. Most of them include the infusion of doses between 350 and 750 mg/kg every 3–5 days for a prolonged period of time. A thorough review of one of these protocols is provided by Mirikova et al from the Riordan clinic (Mikirova et al. 2013).

This, however, differs significantly from the original protocol used by Cameron et al. in the 1970s, and published in their landmark papers about the use of high dose IV vitamin C in cancer patients (Cameron and Campbell 1974, Cameron and Pauling 1976, 1978). In these observational studies, without the knowledge of vitamin C pharmacokinetics we have available nowadays, the most employed protocol combined the oral supplementation of several grams of vitamin C with daily IV infusions of 10 g of the agent for 10 days.

It is worth noting that despite the widespread use of high dose IV vitamin C in many integrative practices and clinics around the world, and of the interesting results that most of us constantly witness with the use of this measure in the oncologic patient, the available high-quality evidence on its effectiveness is still scant (Fritz et al. 2014). This precludes a definite and formal recommendation for this type of treatment, since to date there is only preliminary evidence which does not allow drawing strong conclusions about it. Nevertheless, according to this same evidence high dose IV vitamin C appears to have a good safety profile and a potential antitumor activity.

Regardless of the conceptual orientation of the consulted authors (Fritz et al. 2014, Jacobs et al. 2015), there seems to be much more agreement in the notion that high dose vitamin C infusions do play a role in the improvement of the quality of life and in the reduction of symptom severity in oncologic patients. We are optimistic that the years to come will bring substantial improvements in the quality of the evidence, through adequately designed and implemented controlled trials on the use of vitamin C in cancer treatment. This will be crucial not only for the growth and acceptance of the integrative oncology field, but also for the patients who will receive better medical care when infused with high dose vitamin C. Remaining questions dealing for instance with the most responsive tumors, or the optimal schemes of IV vitamin C (doses, rates of infusion, length of the treatment, etc.) still pose significant challenges even for the physician with years of experience in the field of orthomolecular medicine.

The clinical use of high dose IV vitamin C has another interesting chapter in the treatment of infectious diseases. Vitamin C has been used in many different aetiological contexts, but the viral infections are the ones that seem to exhibit a better response when this agent is utilized. Thanks to the laborious work of compilation of Robert McCracken (2004), it is possible to have access to many difficult to find publications in this area (e.g., articles from the 1930s to the 1970s, written by one of the most prominent pioneers in the clinical application of vitamin C, Dr. Fred R. Klenner).

In fact, many natural compounds have been tested in the search for the ability to suppress viral replication. IV vitamin C infusions produce a positive effect on disease duration and reduction of several viral antibody levels. Also from the group of the Riordan Clinic in Kansas (Mikirova

and Hunninghake 2014), the publication of a clinical study of ascorbic acid and EBV infection showed a reduction in antibody titers of EBV EA IgG and EBV VCA IgM during the IV vitamin C treatment.

There are some other observations from the medical literature that serum vitamin C concentrations at the millimolar levels are able to hinder viral infection and replication in vitro. For example, suspensions of herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), and parainfluenzavirus type 2 were inactivated within 24 hours of having been treated at 37°C with 1 mg (5.05 mM) of copper-catalyzed sodium ascorbate per mL. Ascorbate concentrations as high as 10 mg/mL (50.5 mM) demonstrated only a minimum increase in effect on viral inactivation. The loss of infectivity did not alter either the hemagglutination or complement fixation qualities of the antigens (White et al. 1986).

Vitamin C exerts plenty of influences in the immune system function, both from the quantitative and qualitative points of view. As reported by Sorice et al. in their broad review from 2014 covering this topic (Sorice et al. 2014), vitamin C enhances the cytokine production and the synthesis of immunoglobulins in response to infection (Stephensen et al. 2006); up-regulates the activity of NK cells (Ichim et al. 2011); impacts the lymphocytes proliferation in a dose-dependent fashion, with physiological concentrations increasing it and supraphysiological concentrations inhibiting it (Bruunsgaard et al. 2003, Furuya et al. 2008, Calder et al. 2009); polarizes the differentiation toward type 1 response (leading Th0 subset to differentiate to Th1 subset) (Holmannová et al. 2012); and affects both antimicrobial and NK cell activities, lymphocytic proliferation, chemotaxis, and delayed-type hypersensitivity (Zhang and Farthing 2000).

In the same instance but from an opposite direction, inflammation represents an obstacle for the action of vitamin C on endothelilal cells, due to an inhibition of its uptake due to proinflammatory cytokines like tumor necrosis factor-alpha and interleukin-1 beta (Seno et al. 2004). Vitamin C itself has the possibility to modulate inflammatory processes and it consequences (Zhang et al. 2000). For example, high doses of vitamin C may attenuate exercise-induced inflammatory reactions.

Our clinical experience in the use of intravenous vitamin C in the treatment of infectious diseases has led us to observe that the everyday infections in immunocompetent patients (e.g., cases of common cold, mild gastroenteritis, uncomplicated bronchitis) evolve faster and with much less symptoms derived from the infection. This results after a comparison with previous similar infectious episodes referred by the patient or with household contacts or close relatives with the same disease but who did not receive the vitamin C treatment for any reason. In these types of infections one or two vitamin C infusions of 5–10 g have been very useful.

In cases of complex or chronic infections treated in our institution, vitamin C infusions also have an important role. An important difference with the acute but trivial infection, in the chronic ones or the complex acute ones, usually the patient must be injected in a series of occasions during a more prolonged time. Two to five vitamin C infusions of 15–20 g, given every 3–5 days is the customary treatment for an uncomplicated pneumonia (along with other measures from the biological medicine and the proper antibiotic scheme).

In chronic infections like hepatitis C (HCV), a long course of weekly vitamin C infusions of 15–25 g for 6 months, followed by every other week infusions with similar amounts of vitamin C, have been helpful to manage symptoms referred by the patients as infection related (e.g., fatigue, appetite alterations, sensation of dullness in the right upper quadrant of the abdomen). From a small number of patients with chronic HVC infection treated in our institution, in some of them the viral load has responded favorably descending, while in most of them it has stabilized at the previous count for long periods of time, and in some cases (the least) the viral load has ascended.

In other chronic but less complicated infections like the ones produced by herpes virus (herpes simplex virus type 1 and 2), frequent relapses often represent a high burden in patients' daily activities and tend to impact negatively in their quality of life. Our patients with HSV1 or HSV2 related symptoms have had noticeable reductions in the frequency, intensity, and length of the relapses within the first 6 months of treatment with 4–6 weekly vitamin C IV infusions followed by every

other week IV infusions for 2–4 months. The doses of vitamin C applied intravenously in these cases have been from 5 to 10 g per infusion.

Dengue fever is a relatively common reason of consultation in our area of Colombia, given the all-year-round warm weather (on average 26–33°C) with an altitude of 1000 m above sea level and the closeness to the Pacific shore where it is even hotter (on average 26–37°C), much more humid, and at the sea level. In addition to the occasional Dengue case from time to time as a routine scenario, during 2015 and 2016 in Colombia (as in most parts of the northern area of South America) there were pandemics of Chikungunya and Zika viral infections. Although our institution is not a reference center for the treatment of infectious diseases, some patients with these types of viral infections consulted, searching for additional measures others than the ones established by conventional physicians for symptom management. In Dengue, Chikungunya, or Zika cases (confirmed or clinically suspected) our typical IV vitamin C treatment included 2–5 every other day 15–20 g infusions followed by weekly applications for 4–8 weeks. As in other infections treated with biological medicine, patients referred an optimized and quicker evolution when compared to their same case before receiving the aforementioned scheme, or when compared to relatives, friends, or acquaintances of them who were not treated (for any reason).

At this point we consider of utmost importance to clarify that the practice of biological medicine goes far beyond the use of a single and isolated measure like IV vitamin C or even far beyond orthomolecular supplementation alone. In the biological medicine treatment of any viral infection, the vitamin C infusions are carried out in conjunction with other immune enhancing orthomolecular nutrients (for instance, oral vitamin C and oral/IV N-acetylcysteine, L-glutamine, and L-lysine) and also along with other measures from biological medicine like phytotherapeutics (Arena et al. 2008, Ciuman 2012, Lu et al. 2016), complex homeopathics to enhance Th1 antiviral response (Fimiani et al. 2000, Oberbaum et al. 2005, Enbergs 2006, Roeska and Seilheimer 2010), ozone therapy due to its immunostimulant and germicidal effects (Viebahn–Hänsler 2007), and/or neural therapy with procaine 0.5% both to ease the symptomatic burden and to modulate the inflammatory immune response.

In the story of vitamin C treatment in infectious disease, the episode of its use in the common cold is another one characterized by strong opinion struggles in the medical community. The current evidence regarding this issue points toward some already pretty well-established conclusions, but they are derived mostly from studies with oral vitamin C schemes.

According to the Cochrane review (Hemilä and Chalker 2013) on this issue (last updated by Hemilä and Chalker in 2013), there have been several clinical trials with different dosages of oral vitamin C which haven't been able to demonstrate a preventive/prophylactic effect of this supplement on the common cold. In that context 1 g per day of oral vitamin C was evaluated in several randomized and non-randomized trials, not resulting effective to reduce the incidence of the common cold when taken during the coldest months of winter. Although the general population may not achieve benefit from ingesting 1000 mg of vitamin C daily in terms of the common cold incidence reduction, specific populations subject to significant physical and/or thermal (cold) challenges (marathonists, skiers, and soldiers in six studies) may have an average of a 50% reduction in the incidence of this disease (Douglas and Hemilä 2005, Douglas et al. 2007).

Aside from the data on common cold incidence, a reduction of the intensity of symptoms and length of the infection has been seen consistently among those supplemented with oral vitamin C, both in therapeutic and prevention regimens. As a matter of fact, a 14% reduction in the length of colds was observed in children supplemented with vitamin C with a prophylactic intention, while the reduction in adults reached 8% (42). Larger doses have provided greater symptomatic benefit when compared to lower doses, when vitamin C was taken after the symptoms of the common cold had already started (Chambial et al. 2013, Hemilä and Chalker 2013).

In our clinical experience and taking into account the available information on vitamin C pharmacokinetics (Levine et al. 1996, Benke 1999, Levine et al. 1999, Duconge et al. 2008), small (in orthomolecular terms) but frequent doses of vitamin C have proved to be more useful in the case

of an acute infection. This is important since due to the dynamic flow phenomenon in vitamin C kinetics (Hickey and Roberts 2005, Hickey et al. 2005) this type of dose will produce (for a short period of time) peak blood plasma concentrations well above the ones achieved by a consumption of the RDA for vitamin C. Another factor to observe here is a difference in the turnover of vitamin C in healthy subjects versus patients with acute diseases including infection and myocardial infarction, as evidenced in several leukocyte lines (Hume et al. 1972, Bergsten et al. 1990, Chambial et al. 2013, Ferrón-Celma et al. 2009).

The usual scheme we have employed in our clinical practice is 500 mg of vitamin C taken every half hour for the first 2 hours, followed by every hour doses for the next 4 hours, and then every 2 hours for rest of the day. The patient is emphatically instructed to begin taking vitamin C as soon as the first symptoms of the common cold appear (even the prodromal ones). The following 3–5 days the patient takes an average 4–8 doses of 500 mg vitamin C each day, distributed throughout the day. The number of doses per day depends on the symptomatic evolution of the cold, and it is adjusted over time, according to close medical supervision. In patients whose respiratory disease seems to progress despite the described scheme or in those at higher risk (elderly, immunocompromised, or those with chronic respiratory diseases), we have applied a series of 1–3 IV vitamin C infusions from 5 to 25 g (separated by 2–3 days between them). The IV route can also be implemented from the beginning of the disease (usually along with the oral scheme) at the discretion of the attending physician.

Our regimen has been useful to diminish considerably the symptoms of the common cold as referred by the patients, and in some cases the cold has been aborted after the first day or two days of the regimen. Although the described method is not the exactly the same as the one reported by Anderson et al. in an old but well-designed randomized controlled trial (Anderson et al. 1974), it also supports the notion that larger doses are more effective in terms of symptom reduction during the common cold when the disease has already started.

Modern societies have been struggling with vascular disease (both cardiovascular and cerebrovascular) for many decades. Since cholesterol levels and metabolic syndrome were declared as risk factors for the development of atherosclerosis, most of the attention was strongly diverted to pharmacological measures to diminish blood lipids. As shown by Thomas Levy in his controversial but thoroughly researched work (Levy 2006), lipids are an undeniable actor in the movie of cardiovascular disease (CVD) and atherosclerosis, but it is also true that long standing vitamin C deficiency also plays a key role in the process. Structural and functional consequences of chronic low levels of vitamin C influence the quality of connective tissue and thus prepare an ideal terrain for the atheromatous plaque to develop (Levy 2006). Today, the concept of a relationship between this particular nutritional deficiency and CVD has been gaining terrain into the predominant paradigm of lipid as exclusive culprit factor in CVD (Moser and Chun 2016).

On the other hand, taking these concepts from the bench to bedside has not been easy task. Conflicting results from different intervention trials with vitamin C supplements (most of them through the oral route) are without a doubt a considerable obstacle, precluding a universal therapeutic recommendation for the use of vitamin C in primary or secondary prevention in CVD (at least with the currently available data) (Cook et al. 2007, Sesso et al. 2008, Myung et al. 2013).

Anyhow, as pointed out by Tveden-Nyborg and Lykkesfeldt in their interesting review with a section devoted to this issue (Tveden-Nyborg and Lykkesfeldt 2013), the negative results in these clinical trials evaluating vitamin C in CVD could be related to a variety of factors. The factors range from the design of the study (e.g., biased population selection when not using poor vitamin C status as an inclusion criterion), to the potential authors' unawareness of vitamin C nonlinear kinetics (different in many ways to the usual kinetics of medications subject of evaluation in clinical trials), to the concurrent use of several supplements in the population evaluated (prior or during the study itself, resulting in a confounding factor), among others. We share the opinion that this plethora of failed characteristics should be considered before drawing a definite conclusion on this matter, and paraphrasing these Danish authors, "there is a critical need for well-designed large RCTs that

select or offer the possibility to control for entry-level vitC status and also for the many potential co-deficiencies which may interfere with the interpretation of the results." The chapter of vitamin C in vascular disease is far from being closed.

In terms of mechanisms of action in vascular disease, it has long been recognized that due to the preponderant role of oxidative stress in endothelial dysfunction, the uptake of ascorbate and dehydroascorbate, so as the reduction of dehydroascorbate, and the release of ascorbate, may be of great importance in the regulation of local antioxidant capacity of the vascular bed, to preserve nitric oxide (NO) at physiological levels (Mendiratas et al. 1998). Vitamin C influences both on the NO synthase (eNOS) and on the cofactor tetrahydrobiopterin (BH4) are also significant in the NO activity and its potential impact on CVD and hypertension (61). Profound disturbances in NO bioavailability are a common feature observed in various cardiovascular pathologies including ischemic heart disease and hyperlipidemia (Mendiratas et al. 1998, Moser and Chun 2016).

Many other potential mechanisms of action have been put forward in the case of vitamin C in vascular disease according to results in experimental (animal and human) studies (Levy 2006, Tveden-Nyborg and Lykkesfeldt 2013, Moser and Chun 2016):

- Reduction in the monocyte adhesion to the endothelium;
- Limitation of the inflammation process, even at the intracellular signaling level due to reduction in the TNF-α-mediated NF-$\kappa\beta$ activation;
- Prevention of LDL oxidation; enhancement of the activity of lipoprotein lipase (LPL) as a clearing factor for oxidized lipids in the bloodstream;
- Enhancement of vascular smooth muscle cells conditions, resulting in a delayed rate of apoptosis and a controlled rate of proliferation (both important when atherosclerosis has already developed);
- Decrease in blood pressure values.

L-Glutathione (GSH)

Glutathione is probably the most important antioxidant at the cellular level and has a direct participation in multiple specific detoxification pathways, which are essential to protect our cells and tissues against potential damages inflicted by an enormous variety of harmful substances. This antioxidant is ubiquitous, being present to variable extent in all the cells and organs of the human body. Glutathione has a high capacity as an electron donor and a high negative redox potential. These factors, combined with intracellular concentration at the millimolar levels (from 0.1 to 10 mM (Bremer et al. 1981)), give GSH a very efficient antioxidant profile. The usual plasma concentrations, on the other hand, are on the micromolar level.

From the chemical point of view, Glutathione is a linear tripeptide formed in our cells by the amino acids L-cysteine, L-glutamic, and Glycine (denominated technically γ-L-Glutamyl-L-cysteinylglycine). The result is a water-soluble compound with antioxidant properties (Murray 1996). After Glutathione has yielded the electron of the cysteinil portion of the sulfhydryl group, reduced Glutathione (GSH) turns into oxidized Glutathione (GSSG) through its disulfide bridges. This is a reversible and dynamic process. As long as the rereduction of GSSG takes place, a dynamic balance can be established between the synthesis of GSH, its utilization as an antioxidant and/or detoxifying agent, and its recycling from GSSG (Lomaestro and Malone 1995). A tight homeodynamic control of the GSH availability is established both in the intracellular and extracellular compartments (Kidd 1997). In physiological but also in pathological conditions, GSH:GSSG ratio has been considered a major determinant of the global oxidative stress load (Birben et al. 2012). Most of the intracellular Glutathione (>98%) exists in the thiol-reduced form (GSH), the rest being comprised by the oxidized form glutathione disulfide (GSSG), and other several minoritarian glutathione S-conjugates like thioether, mercaptide, or other thioester forms (Ballatori et al. 2009).

Glutathione results particularly important in the liver, where it is highly concentrated in the hepatocytes (up to 10 mM). Other tissues with high concentrations of Glutathione are the spleen, the

kidneys, the crystalline, and blood cells like the erythrocytes and the leukocytes. Its conjugation is the primary mechanism to remove xenobiotics from the reactive oxygen species (ROS) type, some of which are carcinogens. Conjugation and reduction reactions require Glutathione as part of the process. The Glutathione S-transferase enzymes catalyze the metabolic pathways of Glutathione in the cytosol, microsomes, and mitochondria (Raza 2011). The family of glutathione S–transferase enzymes are responsible for quenching and detoxifying many environmental substances, including free radicals, peroxidized lipids, and xenobiotics (a wide variety of environmental toxins, but also medications like antibiotics, among others). The antioxidant responsive element (ARE) mediates the activation of many genes influenced by oxidative and chemical stress, whose promoter includes this particular element (Hayes and McLellan 1999).

GSH has also a role as "secondary antioxidant," given that it also interacts actively in the reduction of most antioxidants. GSH can turn these other antioxidants useful again after they had been oxidized, thus acting as a regeneration factor. Glutathione aids in the recycling of other antioxidants like ALA (Bast and Haenen 1988), and vitamins like ascorbic acid and alpha tocopherol (Birben et al. 2012). These antioxidants in turn help neutralize the free radical damage potentially inflicted to both cell organelles and also DNA.

Many chronic diseases have been linked to an augmented oxidative stress burden and to low glutathione levels (Ballatori et al. 2009). This includes neurodegenerative diseases (like, for instance, Amyotrophic Lateral Sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia), also characterized by an affected GSH metabolism in the nervous system (Bains and Shaw 1997). Nonetheless, the ubiquity and pleiotropy of this tripeptide have made it difficult to establish strong links between its supplementation, a therapeutic potential, and specific diseases. From a theoretical perspective, neurodegenerative disease is one of the most prominent fields for GSH therapy (Bains and Shaw 1997, Zeevalk et al. 2008). A common feature in many of these ailments, including Alzheimer's disease and Parkinson's disease, is GSH deficiency at the neuronal and glial level. Neuronal survival depends on many factors, and GSH brain levels play a crucial role in the nervous system antioxidant defense. This has been postulated as the rationale for the development of therapeutic approaches using GSH replenishment in neurodegenerative diseases (Zeevalk et al. 2008).

The clinical studies about the efficacy of short experimental GSH IV supplementation schemes in Parkinson's disease patients have had mixed results. In 1996 Sechi et al. (1996) reported a 42% reduction in disability according to the modified Columbia University Rating Scale in their observational open-label study. The benefit lasted for 2–4 months, for the small sample ($n = 9$) of early stage, previously untreated Parkinson's disease patients, who received 600 mg of IV Glutathione twice daily for one month. Much closer to our days, a randomized placebo controlled trial was carried out in 2009 by Hauser and colleagues (Hauser et al. 2009) with 21 Parkinson's disease patients who were already in treatment. In this study, the treatment was well tolerated and consisted of 1400 mg IV Glutathion infusions, three times a week for a month. Also, there wasn't any difference in the unified Parkinson's disease rating scale (UPDRS) found between groups, but the authors make it clear that their main objective was not to assess the efficacy of the treatment but its tolerability and potential adverse effects.

As many other unconventional medical practices, IV Glutathione has also received strong criticism from the orthodox medical establishment. This was the type of reaction (Okun et al. 2010) after the publication of the trial from Hauser et al., with reasonable arguments dealing with discrepancies about the research methodology and the interpretation of the results. On the other hand, there were also very subjective arguments like considering the placement of an IV line as some kind of major challenge. It must be noted that thousands of IV lines are placed around the world every day to infuse all types of medications without any major complication. Even many complex conventional drugs can fill that category of "safe IV infusions" in the short term, regardless of their sometimes-disputable clinical effectiveness in the long term (Morgan et al. 2004). In fact, controversial facts and figures for effectiveness are far from being an unusual phenomenon, even for many of the most commonly used and prescribed medications (Leucht et al. 2015).

Also in this discussion (Okun et al. 2010), we consider some other arguments to be very debatable, like demonizing the fact of charging patients out of their own pocket for a medical practice (which in any case it was provided). This is an issue that usually will receive a more bitter criticism if the professional practices any form of unconventional medicine. On the other hand, regular critics of complementary medicine tend to ignore or understate the variety of scientific and medical behavior artifacts known for a long time in academic medicine. Prominent examples are: the influence of the pharmaceutical industry in the way research material is published as scientific articles in journals (Blumenthal et al. 1997, Bekelman et al. 2003, Landefeld and Steinman 2009, *PLoS Medicine* Editors 2009, Doshi et al. 2012); the ever-growing role of contract research organizations (CROs) and corporate sponsorship in clinical investigation (Davidoff et al. 2001, Smith 2005); the payments and fees made to doctors by the same pharmaceutical companies which economically support their research (McCarthy 2014); the overt or surreptitious commercial and economic ties established around the prescription of many conventional medications (Ornstein et al. 2017), a phenomenon not limited to high-cost drugs like biologics and oncologics, but it also includes many newly branded drugs in order to compete in crowded markets (Brodwin 2015).

It is true that most conventional colleagues will use a different mindset to judge the results from a clinical trial of any given medication, depending on the orientation it has (whether it comes from orthodox medicine or from complementary medicine). And so, the other reaction to Hauser and colleagues' study (Hauser et al. 2009) is a case report (Naito et al. 2010) of drug-induced hepatitis in a patient in Japan who received 1200 mg of IV Glutathione daily for 5 months. The alterations in transaminases remitted after 2 months of the suspension of IV Glutathione. Although it is very clear that this type of report is indeed important to construct a more complete safety profile of any medication, it must also be stressed that in our opinion, such an intensive scheme of IV Glutathione does not reflect the usual orthomolecular practice for this measure. The authors suggest that the doses of Hauser et al. study and the ones from their case report (16,800 mg vs. 24,000 mg IV Glutathione/month) are comparable. Not only do we not consider a 42% higher dose to be comparable, but we also emphasize that the length of the treatment in both scenarios is strikingly different: one month in the clinical trial versus 5 months in the case report. In any case, it turns very relevant to take additional control measures and foresights in any treatment scheme that could be considered experimental. If a patient would receive IV Glutathione for such a long period of time, it is strongly recommended to have a complete laboratory check up every month and any other evaluation pertinent to the liver function.

The arrival of a much clearer picture for the role of Glutathione in Parkinson's disease was only possible until recently, after new research was performed on this issue. The judicious work by Mischley and colleagues is proof that the constancy added to the proper conceptualization of a scientific investigation was able to yield interesting results in this matter (Mischley 2011, 31). The low molecular weight of Glutathione (around 307 Da) make this antioxidant an excellent candidate for the intranasal administration with therapeutic purposes (Mischley 2011).

Their first step was to investigate about any potential safety issues for the use of Glutathione in the intranasal presentation (Mischley et al. 2013). Among the thousands of registers in the database of the compound pharmacy which dispensed the intranasal Glutathione, 300 patients were randomly selected and the questionnaire was mailed to them. There were 70 respondents, whose majority had been prescribed intranasal Glutathione to treat three conditions: Multiple chemical sensitivity (MCS) ($n = 22$), chronic sinusitis/allergies ($n = 21$), or Parkinson's disease ($n = 7$). Adverse effects were common (with a lot of heterogeneity among groups), but all of them mild and mostly related to the route of administration of Glutathione (e.g., irritation of the nasal pathways, etc.). The authors highlight that most of the surveyed patients (78%) reported the overall experience with intranasal Glutathione as positive.

After this preliminary questionnaire-based evaluation of the safety of intranasal Glutathione, the next step by the group led by Mischley was to set up a double-blind, placebo controlled trial (Mischley et al. 2015) to gain further insight about the safety and tolerability of this measure in Parkinson's disease patients.

Thirty patients were unevenly allocated in 4 groups: two treatment groups with different intranasal Glutathione doses (300 and 600 mg/day) of 10 patients each, one placebo group (sterile saline was used) of 10 patients, and one watchful waiting group of 4 patients. The highest Glutathione dose of 4200 mg/week matched the one used in the study by Hauser et al. from 2009 (Hauser et al. 2009). During the 3 months of the intervention period, the patients were instructed to use the nasal spray with either Glutathione or placebo 3 times daily, and they should also keep a daily log of events in which they recorded a report on medication use and changes in symptoms (systemic and local) and general well-being according to validated scales (Monitoring of Side Effects Scale, MOSES and the SinoNasal Outcomes Test, SNOT-20). Laboratory evaluations including blood chemistry, complete blood count, and urianalysis were obtained at several points during and after the intervention (weeks 2, 4, 8, 12, 16). Besides the evaluation of the side effects (both positive and negative), the authors decided to include an assessment of the Parkinson's disease evolution during the study as well. For this purpose, UPDRS scores were used (also considered as a safety measure).

The treatment was well tolerated in both doses, without any statistically significant difference in comparison to the placebo group, both in the clinical and laboratory evaluations. This reflected the findings from previous studies (Hauser et al. 2009, Mischley et al. 2013) regarding the excellent profile of tolerability of Glutathione in Parkinson's disease patients. Aside from that, the authors report a slight clinical improvement according to the UPDRS symptoms scores in the two treatment groups over the placebo group. This trend persisted in the post hoc analysis of the results after the exclusion of the patients who changed medications throughout the study. According to their findings, which included a clinical response superior to placebo, without ignoring the fact of power limitations of this experimental design, Mischley et al. suggest the use of a delayed-start trial (or a similar) design in future investigations to determine a potential neuroprotective effect of intranasal Glutathione in Parkinson's disease. A compilation of the interesting works of Dr. Mischley can be found for further reading in her PhD thesis (Mischley et al. 2016).

Reproaches to the therapeutic use of Glutathione in the context of neurodegenerative diseases have been somehow repetitive (Schulz et al. 2000, Zeevalk et al. 2008, Okun et al. 2010). The controversy has revolved around the uncertainty about if the drug actually crosses the blood–brain barrier and if it does reach the central nervous system (CNS) in levels significant enough to generate any plausible biological or therapeutic activity. To address this problem, Mischley and colleagues carried out a proof-of-concept study using proton magnetic resonance spectroscopy (^{1}H-MRS) to measure the CNS uptake of Glutathione after intranasal delivery in a group of 15 mid-stage Parkinson's disease patients (Mischley et al. 2016). The results of this small pilot study consistently showed an augmentation of the GSH signal in ^{1}H-MRS brain after one single 200 mg intranasal dose. According to the authors, these preliminary findings warrant a more robust trial to evaluate the pharmacokinetic profile of intranasal Glutathione in a larger sample of patients with neurodegenerative diseases. Such a trial could provide information about the magnitude and duration of the increase of Glutathione in the CNS, and about the eventual repercussion of these variables in the efficacy of its use in Parkinson's disease. It could also allow optimizing Glutathione delivery techniques, dosing schedules, product stability, and intranasal formulations.

Glutathione supplementation has also been the subject of evaluation in other conditions outside the spectrum of the neurodegenerative diseases worsening with aging. In some clinical trials evaluating this antioxidant in chronic conditions characterized by a high load of oxidative stress (like cystic fibrosis, e.g. (Visca et al. 2015) or autism (Kern et al. 2011)), the use of oral Glutathione was able to induce changes in systemic oxidative stress biomarkers. It also showed benefits in particular aspects affected by the respective disease. Bear in mind that patients in these studies received Glutathione in oral high doses along with other routes of administration (e.g., intranasal or intradermal). Since there was a combined route of administration, the benefits observed cannot be attributed solely to oral Glutathione. In fact, given that the availability of GSH after the oral ingestion has produced conflicting results, and according to the aforementioned findings by Mischley and colleagues

(Mischley 2011, 2016, Mischley et al. 2013, 2015) about intranasal GSH, it is much more likely that the therapeutic action can be attributed to this way of administration.

Some important considerations must be noticed when supplementing Glutathione with a therapeutic perspective. First, many studies point out to the fact that achieving satisfactory blood levels after the ingestion of Glutathione is not reliable in the clinical practice (Witschi et al. 1992). Basic studies carried out in rodents in the early 1990s showed an increase in the concentrations of Glutathione after an oral load of the antioxidant, both in plasma (circulating free and protein-bound Glutathione) (Hagen et al. 1990) and in tissues (kidney, liver, brain, heart) (Aw et al. 1991).

In spite of these data, this situation does not seem to be replicable in humans and so it has long been known that Glutathione has a poor bioavailability after the oral supplementation (Hagen et al. 1990, Witschi et al. 1992), limiting its use as an oral therapeutic agent. The proteases in the small intestine carry out the protein digestion process, breaking down the Glutathione tripeptide into its basic constituents (just in the exact way it happens with all other peptide/protein chains). It has already been postulated that a possible explanation for the conflicting results about the eventual lack of effectiveness of GSH supplementation in clinical trials could rely on the lack of discrimination of individuals with high/poor antioxidant reserve among the sample of patients included in intervention studies to evaluate this measure.

In this regard, the limitation of an effective oral supplementation of GSH seems to be especially true for healthy adults. In this group, the alleged oxidative stress should not be high, at least from a theoretical point of view. For example, a 4-week protocol consisting of 500 mg of oral Glutathione taken twice a day, failed to induce any significant change in oxidative stress biomarkers in a randomized controlled trial including 40 healthy volunteers (Allen and Bradley 2011). In this study, the blood levels of GSH, GSSG, and the ratio of GSH to GSSG (as an indicator of oxidative stress) remained unchanged both in placebo of oral GSH group. In this same direction, Witschi and colleagues reported that during a 4.5-hour measurement period after the ingestion of a single high dose of Glutathione (3000 mg), it wasn't either capable of increasing blood concentration of glutathione, nor the one cysteine and glutamate as its primary constituents (Witschi et al. 1992).

The results of both these trials, however, have been found debatable by Richie Jr. and colleagues (Richie et al. 2013, 2015). Regarding Allen and Bradley clinical trial (Allen and Bradley 2011), they call the attention on how potential variations in red blood cells' volume and number can impact GSH levels. Furthermore, there is a disagreement in methodological aspects related to the moment of acidification of erythrocytes, which would eventually compromise the stability of both GSH and GSSG and thus could lead to erroneous measurements (Mills et al. 1994). Regarding Witschi and colleagues' publication (Witschi et al. 1992), they call on the attention about the short half-life of Glutathione (only 1–2 minutes), which makes it practically impossible to find an increase in its blood levels after a single oral dose (Kleinman and Richie 2000). Studying the pharmacokinetics of GSH (Aebi et al. 1991), other authors found a longer half-life for its high-dose IV infusion in healthy volunteers. Despite not having the enteric absorption as hindrance, and thus going directly through the blood stream and from there to the cells, IV high-dose Glutathione half-life remains always within the minutes' range (14.1 ± 9.2 min).

In contrast to these results there have been indeed some studies demonstrating an elevation of GSH levels after its oral supplementation. One example is the recent publication by the group of Richie Jr and colleagues (Richie et al. 2015) in which a much longer period of oral Glutathione supplementation (6 months) was able to demonstrate a significant rise in its plasmatic levels compared to placebo. In this clinical trial, 54 healthy adults were randomly divided into three groups: two treatment arms with differential doses of 250 mg/day and 1000 mg/day of Glutathione, and a placebo group. GSH was measured in several compartments and cell types at baseline and at 1, 3, 6, and 7 months (after 1 month of washout). Measurements included GSH in plasma and whole blood, lymphocytes, erythrocytes, and exfoliated buccal mucosal cells. Also, different immune response tests were performed. Phagocytosis and respiratory burst were assessed in neutrophils at baseline and at 3 and 6 months; NK cell cytotoxicity and lymphocyte proliferation was evaluated at baseline and at 3 months.

Both GSH doses produced changes in some of the parameters tested. For instance, regarding GSH levels in whole blood, low-dose and high-dose participants exhibited an increase at 1, 3, and 6 months of GSH supplementation. In other compartments (erythrocytes, plasma, and lymphocytes) mean GSH levels significantly augmented 30%–35% after 6 months of 1000 mg/day GSH. In exfoliated buccal mucosal cells obtained after a mouth rinse with distilled water and brushing of the cheeks and gums with a soft tooth brush, a significant 260% increase was present in the high-dose group. For the low-dose group (250 mg/day of oral GSH), whole blood GSH levels increased significantly (17%), a situation that was also evident in erythrocytes (29%). The authors also report a decrease in the oxidative stress of the supplemented participants, due to the significant reduction in the GSSG/GSH ratio induced in both low- and high-dose GSH dose groups. Moreover, after 3 months of oral GSH supplementation NK cell cytotoxicity increased in both dose groups, but only the high-dose GSH group reached a significant level of increase. In this immune parameter, the authors declare that larger sample sizes and longer evaluation times are necessary to generalize these findings. Except for the patients in the high-dose group, whose GSH levels remained significantly greater than baseline after the washout period, most of the evaluated parameters after GSH oral ingestion returned back toward baseline levels at the 7th month measurements. This would suggest the need for a permanent GSH supplementation if therapeutic/antioxidative action is desired.

In our experience, the use of IV Glutathione in the context of diseases characterized by an elevated oxidative stress burden has provided an interesting tool to enhance the potential antioxidant effects of IV infusions. This concept is applicable (at least from a theoretical perspective) when GSH is injected along with other orthomolecular medications sharing this profile, like vitamin C, ALA or Coenzyme Q10. In our patients, the doses have ranged from 200 mg to 1 g of IV Glutathione, 600 mg being the most common one. GSH is infused through a peripheral vein, diluted in saline solution (volumes of 200–400 mL), using a slow to moderate drip (40–60 drops per minute), and according to the individual tolerance (more on that below). Such antioxidant IV drips have resulted in faster recoveries from day to day infections. In other clinical situations, like chronic diseases, after the regular antioxidant drips including GSH some patients have referred a transient subjective sensation of better overall performance for their daily activities. This energy boost was felt both in the mental and the physical domains and lasts 2–5 days on average.

Although the concomitant use of vitamin C with GSH can be recommended in many pathological states, it has been discussed if this notion can be considered universal. Oncologic disease is one of the areas where this postulate has been put to debate. The Glutathione paradox in cancer has been exemplary described by Traverso and colleagues in their 2013 paper: "While GSH deficiency, or a decrease in the GSH/glutathione disulphide (GSSG) ratio, leads to an increased susceptibility to oxidative stress implicated in the progression of cancer, elevated GSH levels increase the antioxidant capacity and the resistance to oxidative stress as observed in many cancer cells" (Traverso et al. 2013). This poses interesting questionings about the role of GSH either as a potential treatment against cancer or as a cancer cell protector.

Based on years of clinical practice Dr. Harald Krebs, an experienced author from the field of complementary medicine, published protocols (Krebs 2010) using high-dose IV vitamin C (intended as a pro-oxidant) along with IV Glutathione, doses ranging from 1200 to 2400 mg (intended as an anti-oxidant). Even coming from the conventional medicine, there are several reports about the use of IV GSH for the enhancement of chemotherapy tolerability (Smyth et al. 1997). The concept of GSH as a protective agent against chemotherapy adverse effects in ovarian cancer patients treated with Cisplatin had already been propounded more than a decade before (Zunino et al. 1983, 1989, Oriana et al. 1987, Aebi et al. 1991). Initially GSH was conceptualized as a renal protective measure in tumoral rodent models (Zunino et al. 1983, Tedeschi et al. 1990), but the protection it provides against chemotherapy related neurotoxicity and ototoxicity was found out and investigated in the years afterward (Cascinu et al. 1995).

Intravenous GSH can also provide protection against damage inflicted by therapeutic radiation. This was assessed in a randomized pilot trial of patients who had been operated of endometrial

tumors and were then scheduled to receive pelvic radiation therapy (DeMaria et al. 1992). The protocol included the intravenous administration of 200 mg of GSH or saline solution as placebo, performed 15 minutes before the pelvic radiotherapy sessions. Even though DeMaria and colleagues mention that their sample size does not allow to show significance, the patients who received IV GSH had less diarrhea (28% vs. 52% in the control group receiving chemotherapy alone), one of the most common adverse effects of pelvic radiation. Additionally, the IV GSH group had a greater chance to finish the complete cycle of Cisplatin-based chemotherapy (71% to 52%). As with many other chemotherapy schemes, failure to get complete cycles of Cisplatin has been associated with less partial/complete disease remission and/or more disease relapses. As in some other GSH-related publications in the field of oncology, the authors considered that it was unlikely for the antioxidant to interfere with Cisplatin (although this asseveration was not derived patient outcomes).

The issue of a direct potential role (whether inhibiting or promoting) for the simultaneous use of antioxidants with any of the conventional oncologic treatment options is probably one of the most controversial ones in unconventional medicine, and has been largely debated in medical and lay literature (Ladas and Kelly 2009). One of the papers cited as landmark by conventional oncologists who advise against the use of antioxidants by cancer patients is the one poorly done by Dr. Gabriella D'Andrea (2005). It appeared in *CA: A Cancer Journal for Clinician*s, a peer-reviewed journal published for the American Cancer Society, whose own Submission Guidelines acknowledge that "most CA articles are solicited reviews" (American Cancer Society 2017), raising doubts about the impartiality and objectivity of the editorial line of this journal. The particular D'Andrea paper led Ralph Moss to develop a thorough review on the issue in 2006 (Moss 2006), and probably influenced the posterior evaluations on this controversy published by Dr. Keith Block et al. (2007) and by Dr. Charles Simone et al. (2007a,b) in 2007.

This discussion is very complex indeed and goes far beyond reduced Glutathione; there are dozens of different antioxidants with a variety of chemical responses in the host. Besides, there have been interesting arguments both for and against the combination of antioxidants with conventional treatment schemes. In any case, as it has been consistently reported in the medical literature, most publications show that the groups of patients receiving chemotherapy and/or radiotherapy do not only have fewer complications derived from these conventional treatments, but also in many cases their survival time and disease-free time statistics have been longer than the patients who were under conventional management only. These concepts can also be applied to the utilization of IV GSH as a complementary measure in the oncologic patient.

Of course, some studies report a diminishment of the cytotoxic activity of chemotherapy when used in conjunction with GSH. These publications come mostly from the basic experiments in this issue (in vitro and in vivo). Chen and colleagues report their findings after supplementing ascorbic acid, GSH, or their combination in cancer experimental models. When GSH was added to ascorbic acid, cytotoxicity in cancer cells mediated by H_2O_2 production was reduced from 10% to 95% in comparison to the vitamin C alone. The authors conclude that GSH should not be co-administered with ascorbic acid in the context of oncologic treatments, since most cancer cells presented a cytotoxic response to pharmacologic ascorbic acid in concentrations easily achieved in human treatments (IC50 less than 4 mM) and this response could be affected by GSH when given together (Chen et al. 2011).

There are important considerations to take into account before considering Chen's et al. conclusions as fully valid. As noted by Dettman and colleagues in response to Chen's et al. work (Dettman et al. 2012), a closer analysis of their experimental model shows a clear disparity between the amount of GSH and vitamin C used in the in vitro part of the experiment and the one infused to the mice in the in vivo stage. For example, the quantity of GSH infused to the mice would be equivalent to 48 g of GSH if a proportional dose would be used in a 60-kg human. Extrapolation of basic studies' results to the clinical practice is never an easy task. But, when the infused GSH doses used in the in vivo experiments are equivalent to 20–40 times more GSH in comparison to the usual doses used in the orthomolecular clinical practice, this frankly impedes any extrapolation of these

results to any real-world scenario. There are other reasons for criticism highlighted by Dettman et al., but they go beyond the purpose of this section of the chapter.

According to our clinical experience in the use of IV GSH (L Glutathione R 200 [200 mg/2 mL] and L Glutathione R 600 [600 mg/5 mL], HeilPro DKN, Cali, Colombia), we consider important to mention that when this antioxidant is added to an IV drip, it can be painful for some patients. This is a dose-dependent phenomenon, and the nuisance can be avoided or at least diminished using larger diluent volumes, slowing the velocity of the drip, or both. In some unusual but eventual cases, the aforementioned simple measures have not been effective enough. In these patients, the injection of a slow bolus of 2 mL of 1% procaine (not in the neuraltherapeutic sense but with local anesthetic purposes for the sensitive nerve endings in the vein wall) has been successful for the control of the local venous discomfort.

Taking into consideration the difficulties found with the GSH supplementation to obtain reliable elevations in GSH levels in humans, some authors began using N-acetylcysteine (NAC) as a way to induce GSH metabolic pathways and GSH raise as a consequence. While this has been tried successfully in diverse reports, a completely satisfactory definition of the profile for NAC as an antioxidant by itself is still lacking. Although at this time it is very clear that NAC acts as a precursor for building GSH (in fact, it is considered its limiting amino acid), its own activity as antioxidant should not be considered strong. Given the conflicting results of NAC supplementation in clinical settings, some authors (Rushworth and Megson 2014) have suggested that the success in the use of this orthomolecular medication will be relevant only in those cases of actual quantitative cellular deficits of GSH, being unlikely effective in cells with normal GSH repletion. A broader analysis of NAC as a potential antioxidant tool will be provided later in the specific section of this chapter devoted to this amino acid.

Alpha Lipoic Acid (ALA)

Alpha lipoic acid (ALA) is an endogenous antioxidant, also known as tioctic acid. It is synthetized at the mitochondria from cysteine and caprylic acid as precursors. From the chemical point of view, ALA is the 1,2-dithiolane-3-pentanoic acid. It can neutralize reactive oxygen species (ROS) both in aqueous and lipid cellular regions, since it can have lipophilic and/or hydrophilic affinities.

ALA represents an example of a substance that has been transiting the pathway from the orthomolecular field to a conventionally accepted medication for quite some time now. In fact, ALA has gained some recognition in diabetology (Papanas and Ziegler 2014) as a therapeutic measure with a level of evidence (several randomized controlled trials with positive results (Ziegler et al. 1999, Mijnhout et al. 2012)) for the treatment of diabetic peripheral neuropathy. The therapeutic effect of ALA has been linked more than anything to its antioxidant activity.

Studies have attributed four antioxidant properties to ALA (Biewenga et al. 1997):

- The capacity to chelate metals,
- The ability to scavenge reactive oxygen species (ROS),
- The capacity to regenerate/reduce antioxidants (endogenous or exogenous), and
- The role in oxidative damage reparation.

When applied systemically through the IV route, ALA accumulates in tissues and is converted to dihydrolipoic acid (DHLA) by the enzyme lipoamide dehydrogenase. Both forms (ALA and DHLA) are biologically active. There are important differences in the route of ALA supplementation. When ingested ALA rarely reaches tissue concentrations above the micromolar levels. In lower concentrations, it is considered unlikely that ALA can exert direct and primary antioxidant activities in the cells (Shay et al. 2009). This situation changes when ALA is injected directly to the blood stream, allowing higher concentrations. In that case, ALA can scavenge hydroxyl radical, subchloric acid, and singlet oxygen. Moreover, ALA can chelate transient ions. Due to these properties, ALA has been used with variable degrees of success in a variety of chronic diseases, like diabetic

nephropathy, hepatic, cardiovascular, and neurodegenerative diseases according to the article by Huk-Kolega and Skibska (Huk-Kolega and Skibska 2011). Acute and potentially chronic situations, like fungal infections or metal intoxications are also interesting possibilities for the therapeutic utilization of ALA. The aforementioned review surveys the antioxidant ability of LA and its role in pathological states where increased concentration of ROS is observed.

As mentioned briefly in the introduction, diabetic neuropathy is one of the most prominent and investigated indications for the therapeutic use of ALA in the clinical practice. The earliest reports of its use in neuropathic conditions date as early as the last years of the 1950s (Bock and Schneeweiss 1959). According to Ziegler's meta-analysis from 2004 (Ziegler 2004), which included a large sample of diabetic patients ($n = 1258$) from several randomized controlled trials, a class Ia level of evidence can be granted to ALA for the treatment of this condition. The protocol of daily IV infusions with ALA at a dose of 600 mg/day over a 3-week period has been considered safe and effective to achieve a clinically meaningful reduction of peripheral neuropathic symptoms in diabetic patients (Bock and Schneeweiss 1959, Ziegler and Gries 1997). The favorable effect of IV ALA on neuropathic symptoms was associated with an improvement in neuropathic deficits. For the author of this meta-analysis, this clearly suggests a potential role in the enhancement of the underlying neuropathy. Diabetic neuropathy also affects the autonomic portion of the nervous system, causing cardiac dysfunction. Oral treatment with ALA at doses of 800 mg/day taken for a period of 4 months was able to improve this condition in non-insulin dependent diabetic patients (Bock and Schneeweiss 1959, Ziegler and Gries 1997), when evaluated through cardiac variability measures.

High blood pressure is another frequent component of metabolic disease. Some studies have been carried out to evaluate a potential usefulness of ALA in hypertension. With a hypothesis revolving around the role of the mitochondria and its derived oxidative stress in vascular disease, ALA was evaluated in combination with acetyl-L-carnitine in a double blind, crossover, placebo controlled trial (McMackin et al. 2007). In the group of 36 patients with previously known coronary artery disease, 8 weeks of the active treatment with this combination were able to induce a significant reduction in systolic blood pressure. This effect was more significant both in the subgroup of patients with blood pressure above the median and in the ones with metabolic syndrome. In addition to these functional changes, the active treatment also achieved a reduced arterial tone, interpreted from a significant increase in brachial artery diameter of 2.3%. The clinical utility of this preliminary finding, so as the confirmation of the effect in larger clinical trials is still awaited, according to the authors.

It is interesting how biological medicine can be integrated into conventional medical practice. Many diabetic patients have associated hypertension. This group of patients shows good response to angiotensin converting enzyme (ACE) inhibitors which have multiple advantageous characteristics. In them Quinalapril, for example, reduces blood pressure, proteinuria, and improves endothelial function. Although the addition of ALA to Quinalapril was not able to generate a further reduction in blood pressure levels (beyond the one produced by Quinalapril alone), it potentiated the decrease in the proteinuria and the endothelial-dependent flow-mediated dilation in a crossover, double blind study (Rahman et al. 2012). Rahman and colleagues from the Cardiology Division at Emory University School of Medicine consider that these results could represent a potential hamper for the usual deterioration of the vascular bed observed in hypertensive diabetic patients.

In experimental models of high blood pressure, long-term treatment with ALA decreased blood pressure in hypertensive animals, without significant changes in baseline heart rate. Baroreflex has sympathetic and parasympathetic components, whose sensitivity was increased after the ALA treatment. Normotensive animals were also treated with ALA, but did not experience changes in any of the parameters evaluated. Regarding their results, Queiroz et al. suggest that long-term supplementation of ALA exhibits an antihypertensive effect and improves baroreflex sensitivity in rats with renovascular hypertension (Queiroz et al. 2012).

Antioxidative properties have been proposed as the possible explanation for the ALA mechanism of action on the prevention of the development of hypertension and hyperglycemia. Midaoui et al.

(2003) assessed the effect of ALA supplementation on the prevention of an increase in heart mitochondrial superoxide anion production and in advanced glycation end-products (AGE) formation in the aorta of Sprague Dawley rats. The experimental rats had developed high blood pressure, hyperglycemia, hyperinsulinemia, and a 4-fold increase in an insulin resistance index after having been fed with a 10% D–glucose solution additional to their chow diet. The group of rats supplemented with ALA in conjunction with the hyperglycemic diet did not develop hypertension, nor was AGE accumulated in their aortas, nor augmented the production of superoxide in the mitochondrias of myocardial cells.

In the wide spectrum of possibilities of metabolic syndrome, some patients will express it also as non-alcoholic fatty liver disease (NAFLD). Long-term supplementation of ALA in rats resulted in prevention of NAFLD development, through a series of mechanisms. The effects include a reduction in hepatic alterations which characterize the disease, like steatosis, oxidative stress, immune activation, and local inflammation (Jung et al. 2012).

Alzheimer's disease is one of the most problematic degenerative diseases of the nervous system. In data from basic studies including cell cultures and animal models, it has been shown that a mixture of ALA with nutraceuticals like docosahexaenoic acid (from fish oil), curcumin (from Curcuma longa), and (-)-epigallocatechin gallate (from green tea) act synergistically to reduce generic aspects like oxidative stress and inflammation, but also specific aspects like amyloid beta levels and amyloid beta plaque load. An Australian group of authors led by Maczurek reviewed the diverse mechanisms of action of ALA in Alzheimer's disease, possible dosages and schemes derived from ALA pharmacokinetic data, and its possibilities as a treatment of this type of dementia (Maczurek et al. 2008).

In the complementary treatment of dementias, most beneficial effects have been linked to the use of the reduced form of lipoic acid, named dihydrolipoic acid (DHLA). Holmquist et al. (2007) inform about the possibility to use R-alpha lipoic acid instead of DHLA, as it is reduced by mitochondrial lipoamide dehydrogenase, a part of the PDH complex. They explore the therapeutic properties of lipoic acid, with particular emphasis on its R-alpha-enantiomer, to treat Alzheimer's disease and related dementia.

ALA can also be utilized in the field of clinical toxicology. ALA and other antioxidants have a role in the detoxification of heavy metal poisoning. One of the main problems with heavy metals is that they cause oxidative deterioration of many crucial bio-molecules, like nucleic acids (DNA and RNA), proteins and lipids through chain reactions mediated by free radicals. It has been proposed that ALA constitutes a preventive and also therapeutic measure in cases of cellular damage related to unsustainable loads of oxidative stress and derived from heavy metal intoxication (Veljkovic et al. 2012, Flora et al. 2013).

As reported by Xu and colleagues in a model of experimental cadmium exposure (Xu et al. 2015), ALA significantly protected cadmium-treated HepG2 cell cultures against cytotoxicity and lipid peroxidation, and it was able to reverse cellular GSH deficit ($p < 0.05$). The authors also reported an increase in the activity and the expressions of glutamate cysteine ligase (γ-GCL), a limiting critical first step enzyme in the glutathione metabolism.

We have experience with the use of injectable ALA in doses ranging from 30 to 300 mg, diluted in a solution bag and mixed with other orthomolecular nutrients and antioxidants. It is compatible with normal (0.9%) saline solution or with Ringer's lactate. We used to drip it along with vitamin C based IV infusions or along with mineral/trace element-based IV infusions. There are several presentations available in our countries:

- Ácido Alfa Lipóico (10 mL vials)
  30 mg/mL, for a total of 300 mg/vial, HeilPro DKN—Cali, Colombia
  2.5%, for a total of 250 mg/vial, Farmacia Milenium—Buenos Aires, Argentina
- Ácido Alfa Lipóico (2 mL ampoules)
  25 mg/mL, for a total of 50 mg/ampoule, MediBio—Bogotá, Colombia

- Ácido tióctico (10 mL vials)
  250 mg, Farmacia Francesa—Buenos Aires, Argentina
- A—Lipo R™ (24 mL vials)
  600 mg, Nutrabiotics—Bogotá, Colombia
- SAOX (50 mL vials)
  Includes 300 mg ALA + 1 gram of GSH + 9 grams of ascorbic acid, HeilPro DKN—Cali, Colombia

Normally IV ALA is well tolerated, but some precaution must be taken about the possibility of hypoglycemia during its infusion. This is a dose-dependent effect, rarely seen in doses below 120 mg. The glucometry values have been around 40–60 in these cases, and came accompanied by symptoms such as mild chills, blurred vision, or mental fogginess. It must be remembered that the use of glucometry to evaluate potential hypoglycemia in this context is limited in vitamin C-based infusions, since ascorbic acid can cause false positive alterations of this laboratory parameter. In that case, it should be the clinical picture that will guide the medical conduct with respect to the situation.

In any case, faster infusion rates, lower dilution solution volumes, and/or the concomitant use with the antioxidant DMSO or with medications like insulin or oral hypoglycemic agents could eventually act as potentiating factors. Simple measures are usually enough to prevent this phenomenon: the patient is instructed to ingest some food in the hour prior to any orthomolecular IV infusion. In the occurrence of hypoglycemia despite this measure (in sensitive patients), a slow bolus of 15–25 cc 5% dextrose has proven corrective of the symptoms associated with the disturbance of carbohydrate availability. Another recommendation to avoid IV ALA related hypoglycemia is to escalate the dose in a progressive manner, beginning with 100 mg and adding 100 mg every infusion (Nutrabiotics 2016), until reaching the objective of 600 mg of IV ALA in the case of neuropathy orthomolecular treatment.

Dimethyl Sulfoxide (DMSO)

Dimethyl sulfoxide (DMSO) is an amphipathic molecule, characterized by being a polar aprotic solvent miscible in water, but also in many different substances, both aqueous and organic. Besides water, DMSO is also soluble in acetone, ethanol, benzene, diethyl ether, and chloroform. It can act as a good solvent for unsaturated, nitrogen-containing, and aromatic compounds. Considering the hygroscopic properties of DMSO, it should be kept in sealed containers. DMSO has wide applications in the fields of biology and medicine (Walker 1993).

From the physico-chemical points of view, at room temperature DMSO can be found as a clear, colorless, and oily liquid, which distinctive characteristic is a more or less (depending on the concentration) noticeable bitter smell and taste, often referred to as garlic or vegetable-like (Wood and Wood 1975).

DMSO is a potent antioxidant/reactive oxygen species (ROS) scavenger and this is one of its main capabilities (Brayton 1986). It has been utilized for decades by unconventional medicine practitioners due to a variety of purported therapeutic actions. Dr. Stanley Jacobs, a surgeon affiliated with the Medical School at the Oregon Health Sciences University along with Dr. Robert Herschler, a chemist affiliated with Crown Zellerbach Corporation, were the pioneers for the introduction of DMSO in medicine as a therapeutic agent (Walker 1993). When searching for a better preservation agent in the context of transplant surgery, Jacobs came across this quite peculiar substance, which played an excellent role as a low-toxicity cryoprotectant for a variety of cells and tissues, thus allowing its prolonged storage at subzero temperatures.

Many of the properties of DMSO with a therapeutic potential made themselves evident even from the beginning (Wood and Wood 1975, Swanson 1985), in different biology experiments and basic sciences investigations. In the medical literature (Swanson 1985, Santos et al. 2003) DMSO is mentioned as an anti-inflammatory agent and topical analgesic, cell-differentiating inducer,

cholinesterase inhibitor, hydroxyl radical scavenger and antioxidant, hydrogen-bound disrupter, topical analgesic, carrier for topical application of pharmaceuticals, cryoprotectant for tissues and cell conservation, and solubilizing agent used in sample preparation for electron microscopy, intracellular low-density lipoprotein-derived cholesterol mobilizer, intercellular electrical uncoupler, and also as an antidote to avoid the consequences of extravasating of vesicant oncologic medications (Kassner 2000).

During the first decades after the introduction of DMSO as a therapeutic tool, there were concerns about the potential toxicity it could bring when used for the treatment of humans. These concerns arose mainly from early observations in some animal studies reporting lenticular refractive changes in diverse species like dog, rabbit, swine (Rubin and Barnett 1967, Smith et al. 1969), and guinea pigs (Rengstorff et al. 1972). It results central to note that these ocular adverse effects are species-specific phenomena, and hence have not been able to be reproduced in primates nor in humans (Smith et al. 1969, de la Torre et al. 1981).

Moreover, the ocular safety of DMSO was specifically addressed in the study by Shirley et al. in 1989 (Shirley et al. 1989). In this randomized, double-blind trial, 84 patients with hand ulcers secondary to systemic progressive sclerosis (scleroderma) were divided into three groups to receive either topical 70% DMSO, topical 2% DMSO, or 0.85% normal saline solution as control. The treatment consisted in immersing the patients' hands into these solutions, three times per day for three months. For the results to be comparable to the doses previously used in animal studies, a theoretical maximum dose of 2.6 g DMSO/kg/day was considered. From the 55 patients who completed the study protocol, 46 went through a complete ophthalmologic evaluation before the immersions, and at 12 weeks after finishing the protocol. The ophthalmologist evaluated personal and familiar ocular history, past drug history, and performed pupillary examination, cycloplegic refraction, motility study, applanation tension, indirect dilated funduscopic examination, and slit-lamp examination. The ocular variables examined (e.g., visual acuity, lenticular changes, and cataract development) did not present any significant change among the three groups during the treatment period. None of the participants in this trial had any lenticular changes like the DMSO-related ones described in several animal studies (Shirley et al. 1989). Other reports in humans and primates (Brobyn 1975) have arrived at the same conclusions, and therefore DMSO is considered a safe drug for human use from the ophthalmic point of view.

We have deliberately decided to divide the description of our experience with the use of IV DMSO in two conceptual modes of use, according to the pursued therapeutic objective.

On the one hand, we used to apply IV DMSO in doses from 30 to 50 mg/kg/infusion as a theoretical carrier for many other nutrients, when dripped together in the same solution bag. The regular doses in this context range from 2 to 4 g of 99.9% DMSO into 200–250 mL of normal saline solution, along with other orthomolecular supplements. The final concentration of DMSO in this type of orthomolecular IV drip is 1%–2% on average. This can be infused every week to every 4 weeks, depending on the suspected or confirmed nutritional deficiencies, or according to the clinical necessities of the patient. Apart from the properties that DMSO can have on its own, it has also been largely known due to its ability to carry molecular from one compartment to another. In this sense, DMSO potentially binds to minerals, amino acids, and vitamins, and carries them from the intravascular compartment to the interstitial compartment, and from there to the intracellular space. In a reversible process, it has been shown how varying concentrations of DMSO are able to cross body membranes in animals (Wood and Wood 1975).

On the other hand, we have employed much larger doses mostly in the treatment of structural pain (joints, muscles, and bones). Such a medical use of DMSP has been described for many decades already (Demos et al. 1967). In our experience 200–250 mg/kg/infusion of IV DMSO works well and it is perfectly tolerated, but doses up to 1 gr/kg/infusion have been reported in the literature (Walker 1993, Olszewer et al. 2017). It must be noticed that the volume of physiologic saline to prepare the drip bag, so as the total infusion time both have to be augmented proportionally. A typical example of an orthomolecular treatment of this type would be to add 12 cc of 99.9% DMSO

to 360 cc of normal saline solution for a 60-kg patient, to be dripped approximately in 2 hours (60 drops per minute). In this example, the final concentration of DMSO is 3.3%. Usually this is mixed with other orthomolecular supplements, depending on the clinical objective of the patient. In the search for a better aid in structural pain control, other orthomoleculars like magnesium chloride 20% (2–5 cc), cyanocobalamin 0.1% (2–4 cc) and/or L-phenylalanine 2.5% (1–3 cc) would be good examples.

Patients with diseases like rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis (Eberhardt et al. 1995) quite often get a lot of symptomatic relief from serial IV DMSO infusions. This type of infusion is usually repeated much more often than the ones first described in the previous paragraph, every 3–7 days, depending on the clinical status of the patient. That is especially true at the beginning of the treatment (the first month to 3 months), when the proinflammatory spiral is still spinning its wheel fiercely. Afterward the rest of the measures of natural treatment gain strength in a progressive way. The patient also adopts a healthier way of living and the process tends to get easier, and then orthomolecular IV infusions can be performed less frequently. A healthy alkaline-based diet is one of the cornerstones of this approach, since it makes it difficult for the articular inflammation to thrive (Walker 1993). Analgesic properties of DMSO could rely on the induction of a concentration-dependent blockade of nerve fibers type C, as published by Evan et al. in 1993 (Evans et al. 1993).

Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10) is an endogenous antioxidant molecule. It is also known as ubiquinone (oxidized) or ubiquinol (reduced). As these names suggest, it is present in all the organs and systems of the human body at the cellular (mitochondrial) level. Nevertheless, the concentration of CoQ10 is highly variable between organs, depending on their metabolic rate. In organs like the heart it is present in high amounts (114 ± 9.2 μg/gr tissue), while it is around half of the concentration in organs like the kidney or the liver (66.5 ± 6.6, and 54.9 ± 4.1 μg/g tissue, respectively) (Aberg et al. 1961, Turunen et al. 2004). Chemically CoQ10 is the trans 2, 3-dimethoxy-5-methyl-6-decaprenyl-1, 4-benzoquinone (in the reduced form). CoQ10 is a fat-soluble, vitamin-like compound, which has not been considered strictly essential since it does not necessarily have to be supplemented to be present in cells. Nonetheless, therapeutic action of CoQ10 is achievable mostly with pharmacologic supplemental doses.

The research in CoQ10 had an inflection point by the mid-twentieth century, when Dr. Frederick L. Crane and his team from the University of Wisconsin were able to isolate this antioxidant from cardiac muscle's mitochondria in 1957. One year later in 1958, Dr. Karl Folkers and colleagues of the University of Texas determined the chemical structure of CoQ10. This antioxidant has been used with various degrees of success and evidence in a series of clinical conditions (Garrido-Maraver et al. 2014), as reviewed by Garrido-Maraver and colleagues in 2014.

Considering that the heart is the tissue where CoQ10 is most concentrated in mammals including human beings, the cardiovascular system soon attracted the attention for a potential therapeutic use for this antioxidant. Conditions like high blood pressure (Rosenfeldt et al. 2007), cardiac failure (Belardinelli et al. 2006, Adarsh et al. 2008), ischemic heart disease (Celik and Iyisoy 2009, Ivanov et al. 2013b), and endothelial dysfunction (Belardinelli et al. 2006) (as a common denominator for the others) could be benefited from orthomolecular CoQ10 supplementation. It must be clarified that recent evidence of CoQ10 in hypertension shows that it is unable to lower blood pressure by itself, according to the Cochrane review on the topic by Ho and colleagues (Ho et al. 2016).

In the second half of the twentieth century, the abnormalities in blood lipid levels were characterized as a risk factor for cardiovascular disease. Statins emerged as the main treatment options, and with a wider portion of the population being treated with this type of drug, it became evident that patients on HMG-CoA reductase inhibitors due to blood lipid disorders have lower CoQ10 levels (Hargreaves et al. 2005). Some authors even refer to this situation as an acquired CoQ10 deficit disease (to differentiate it from the genetic inherited CoQ10 deficiencies).

Statins have a variety of adverse effects, myopathy being one of the most worrisome. Not only is muscle pain the most common side effect of statins (present in more than 1% of the patients) but in rare occasions, some patients can advance to severe stages even with rhabdomyolysis. To add confusion to the issue, in a randomized placebo-controlled trial with more than 20,000 subjects, the frequency of muscle pain in patients taking Simvastatin was the same as in those taking placebo (Heart Protection Study Collaborative Group 2002).

Some authors consider CoQ10 supplementation highly recommended in patients on statins in order to prevent the myopathy potentially induced by these medications (Garrido-Maraver et al. 2014), but without forgetting that the evidence regarding this indication for CoQ10 is not yet conclusive due to contradictory results in the trials analyzed (Mas and Mori 2010, Wyman et al. 2010). It has been suggested that some disturbances caused by this type of medication could be prevented or treated by supplementing CoQ10, at least to some extent according to the biochemical links between statins and CoQ10 deficit induction. In the orthomolecular sense, it would mean the reposition of a substance that is lacking in the patient's organism either due to the blockade in a metabolic pathway (like in this case) or due to insufficient cellular production or due to nutritional deficits from its precursors.

Some (conventional) sources even consider that implementing CoQ10 in statin treated patients with myalgia is feasible, mainly as a test and not as a routine measure. Marcoff and Thompson from Connecticut mention its use in myopathic statin-associated patients, given some anecdotal and preliminary evidence of an effect on muscle symptoms, and that there wouldn't be any risk associated with this antioxidant (Marcoff and Thompson 2007). In their opinion, some patients may respond to CoQ10, albeit they give chance only to a placebo effect in those cases.

Intravenous CoQ10 has been used with success limiting the extent of tissue damage in several experimental ischemia animal models. The group led by Prof. Oleg Medvedev from the Lomonosov Moscow State University in Russia has been dedicated to investigate the use of injectable CoQ10 in a variety of ischemic conditions, producing several interesting articles over the years. One of their initial investigations (Gorodetskaya et al. 2010) demonstrated a rapid rise in the plasma and tissue CoQ10 after an IV bolus in experimental rats. The plasma samples, and the cardiac, cerebral, and hepatic tissues showed important elevations of CoQ10, which were maintained in the plasma, heart, and liver after 48 hours, but not in the brain tissue. Some years later, Ivanov and colleagues (Ivanov et al. 2013a) reported significantly less cardiac structural and functional compromise after a single IV dose of CoQ10 in an animal model of myocardium infarction, with irreversible cardiac ischemia (Niibori et al. 1998, Verma et al. 2007). The cardioprotective effect of IV solubilized CoQ10 in a transient ischemia animal model after a single dose had beneficial repercussion on left ventricular lesion and after event function, but only if it was injected 1 hour after the experimentally induced ischemia and not when this measure was applied 3 hours after the event (Ivanov et al. 2014).

Also from this group and based on their previous findings (Gorodetskaya et al. 2010) Belousova and co-workers decided to investigate the action of CoQ10 in acute ischemic brain lesion. They performed an experiment injecting IV CoQ10 into laboratory rats after transient (6-hour arterial occlusion) focal brain ischemia and before reperfusion (Belousova et al. 2016a). The infarction area was reduced and the neurological impairment was milder in the treated animals in comparison with physiologic saline solution injected animals, demonstrating a robust neuroprotective role of CoQ10 in this induced ischemia model. CoQ10 was able to produce a lesser compromise of both functional and morphological markers of brain damage.

A similar neuroprotective capacity of Coq10 was found when the experimental ischemic lesion was irreversible (24-hour arterial occlusion) and the CoQ10 was injected IV in the first hour after the event began (Belousova et al. 2016b). The CoQ10 injected rats evidenced higher levels of the antioxidant in their brain tissue, presented less neurological deficit derived from the ischemia, and had an average of half the size of the infarction areas when compared to the control group (injected with normal saline solution).

CoQ10 also exerted a neuroprotective effect derived from its strong antioxidant and reactive oxygen species (ROS) scavenger properties. This orthomolecular nutrient was effective in the reduction

of the biochemical and histological consequences of another type of experimental brain ischemia model, according to Ostrowski's publication (Ostrowski 2000).

Besides the cerebral ischemia models already detailed, there have been other experiments evidencing a positive role for CoQ10 supplementation in rats with brain ischemia after a head trauma. Kalayci and colleagues from the neurosurgery department at the Zonguldak Karaelmas University in Turkey developed an experimental traumatic brain injury model in laboratory rats and described their positive results after the use of CoQ10 in this context (Kalayci et al. 2011).

The aforementioned preliminary evidence strongly suggests the possibility of a therapeutic action from CoQ10 in acute cardiovascular/cerebral ischemic conditions (from different origins), but it still has to be subject to the proper review in clinical studies (human patients in real life conditions).

There are other systems and organs that can have benefits from a CoQ10 supplementation therapy. Among these, of the most prominent with several indications for its therapeutic use is the nervous system (Morris et al. 2013). As it was commented earlier in the glutathione section, the depletion of antioxidants has been linked to a variety of neurological disorders, mainly the neurodegenerative ones. This also applies to CoQ10, whose potential deficiency may have a role in the pathophysiology of morbid processes like depression, Parkinson's disease (Shults 2005), myalgic encephalomyelitis/chronic fatigue syndrome, and fibromyalgia.

A lot of disease-related aspects can ameliorate through a CoQ10 treatment in nervous system affection (Morris et al. 2013): enhancing the patient's quality of life in Parkinson's disease and fibromyalgia, decreasing depression intensity, reducing hyperalgesia and modulating inflammation hyperactivation in fibromyalgia (Cordero et al. 2014), delaying the progression in Parkinson's disease, improving the global energy levels in myalgic encepholamyletis/chronic fatigue syndrome. It has been postulated that most (if not all) of these effects can be explained by CoQ10 reduction of oxidative stress burden and by the protection to the mitochondria and its electron transport chain.

CoQ10 has been supplemented mostly by the oral route and injectable routes. Its typical absorption after oral intake is slow and limited, in relationship with physical characteristics like hydrophobicity and a relatively large molecular weight (Bhagavan and Chopra 2006, Nishimura et al. 2009). CoQ10 has a low absorption of 2%–3%, needing days to weeks of sustained supplementation to generate an impact in tissue CoQ10 levels. In experimental rats receiving oral CoQ10, some organs like the spleen or liver will show significant elevations of its CoQ10 levels, but in other organs like heart or kidney the levels were low to undetectable (Alessandri et al. 1988). All these limitations are more evident in the powder capsules of CoQ10. This can be partially enhanced when a solubilized form of CoQ10 is used, but the extent of the change is much more powerful (by many times) when CoQ10 is infused through an IV line in an injectable presentation.

The use of the IV route to supplement CoQ10 has some advantages, like the possibility to reach a much higher serum level, that correlates to a higher hepatic level. Due to the much longer period of time, the high levels remain in some organs, there have been some hypotheses about a reservoir for the antioxidant, probably at the hepatic level (Ivanov et al. 2013a) or at the intestinal level (through enterohepatic recirculation, anyway) (Yuzuriha et al. 1983). As mentioned by Bhagavan and Chopra (2006) in their article about CoQ10 pharmacokinetics, phenomena like a second plasma peak after both oral and IV administration led Yuzuriha et al. (1983) to propound a zero-order rate constant rather than first-order kinetics for CoQ10 supplementation (later came Tomono's research with radioactive labeled CoQ10 to expand this concept [Tomono et al. 1986]).

In our practice, we have experience with the use of injectable Coenzyme Q10 (2 mL ampoules with 40 mg, MediBio—Bogotá, Colombia; 0.1% vials of 10 mL, Farmacia Francesa—Buenos Aires, Argentina) at doses ranging from 10 to 80 mg. It is usually added to an antioxidant IV drip in conjunction with alpha lipoic acid and/or glutathione, amino acids, and a base of either multiple minerals or vitamin C. The main indications have been aiding in the recovery period of patients with recent ischemic events (either from coronary or cerebrovascular origin), neurodegenerative disorders (mostly Parkinson's disease), and fibromyalgia patients.

Regarding this last group of patients with fibromyalgia, we have had some whose response to the treatment with other biological medicine's interventions was not satisfactory, but changed radically after implementing the orthomolecular IV infusions (including CoQ10). Other groups have had interesting therapeutic experiences with the supplementation of CoQ10 in fibromyalgia patients (Cordero et al. 2011, 2012).

It is worth mentioning that in patients with fibromyalgia the usual response to a biological medicine treatment has been good to excellent. Most of them experience an important amelioration of their clinical picture 3–6 months after receiving a polymodal treatment including:

- Neural therapy according to Huneke (Dosch 1984) (local and segmental—metameric injections of a local anesthetic, preferably procaine 0.5%) and/or injected local anesthetics but not necessarily in the neural therapy context (e.g., IV drips, mainly lidocaine [Schafranski et al. 2009]),
- Bio-regulatory medicine (medications through the oral route + biopuncture [local and segmental—metameric injections]) (Goldman et al. 2015) (antihomotoxic medications through the oral route + biopuncture [local and segmental—metameric injections]) (Egocheaga and del Valle 2004, Präg 2004),
- Ozone therapy (ozone administered either with local injections, or systemically through an ozonated saline IV drip or through rectal insufflation) (Hidalgo-Tallón et al. 2013, Longas-Vélez 2014, Balestrero et al. 2017),
- Changes in alimentary patterns (toward a vegetarian diet [Arranz et al. 2010], an exclusion diet [Holton et al. 2009], an alkaline diet or a combination of several of these measures),
- An individually tailored exercise routine (Ortega 2016),
- And mind–body medicine techniques (like yoga or meditation) (Wahbeh et al. 2008, Theadom et al. 2015).

Nevertheless, for a few of them this approach was not able to produce an appropriate symptomatic relief, proving to be particularly challenging cases, and it was comforting to finally find relief with the orthomolecular aspect of the treatment. In some of these difficult cases the achieved clinical improvement through the addition of IV and oral orthomolecular supplementation schemes lasted for several months even after the discontinuation of the treatment.

Alterations in micronutrient levels are known to happen in fibromyalgia patients, although the information differs regarding the nutrient. According to the Joustra and co-workers, recent publication (Joustra et al. 2017), for example, while the status of manganese, vitamin B1, vitamin A (in the majority of studies), and vitamin E (studies with methodological issues) resulted consistently low in fibromyalgia patients, other nutrients' status was not statistically different when compared to healthy controls (folic acid, vitamin B12, iron, molybdenum, phosphorus, sodium, iodine, and the majority of studies about potassium and selenium). Some nutrients even showed important discrepancies (increased or decreased levels for the same nutrient) between the different studies analyzed, like it was the case for copper, ferritin, and zinc. Nutrients' role in pathophysiology of fibromyalgia is not completely understood and these deficiencies are not necessarily related to the clinical presentation of this condition (Arranz et al. 2010, Rosborg et al. 2007, Joustra et al. 2017). Within the scientific community, the notion of an orthomolecular origin of fibromyalgia or its use as a complementary measure treatment in fibromyalgia in order to aid in the patient health care is not free of controversy and some authors consider it unnecessary or lack merit (Rosborg et al. 2007, Joustra et al. 2017).

Amino Acids

Amino acids are organic molecules consisting of C, O, and N, and constitute the basic unit in the formation of proteins, one of the main components of the organic functions and structure. Proteins are among the most important substances in nature; in human health, they have notorious and

variated roles, since enzymes, hormones, neurotransmitters, cytokines, albumin, collagen, and many others are proteins.

Although there is an undeniable importance of proteins, science and medicine have begun to appreciate the useful roles that have single amino acids or short dipeptidic/tripeptidic molecules. L-glutathione, which was covered earlier in this chapter, is a clear example of this. In this section, we will address single amino acids as therapeutic tools.

Amino acids are obtained from their ingestion and from their synthesis in the human organism. The liver must process and produce about 60% of the amino acids in our body. The remaining 40% depends on the diet protein content and the ability to degrade these proteins into smaller peptidic chains, tripeptides, dipeptides, and single amino acids. Afterward these must be absorbed in the digestive tract and then it can reach the blood stream, the hepatic metabolism, and the tissues.

N-Acetylcysteine (NAC)

Acetylcysteine is the N-acetylated form of the amino acid L-cysteine. As it has been extensively explained in the antioxidants section, it is the limiting precursor in the formation of the antioxidant glutathione in the tissues and cells. The thiol (sulfhydryl) group from L-cysteine confers NAC its antioxidant capacity, since this group has the possibility to reduce reactive oxygen species (ROS) (Mokhtari et al. 2017).

After an oral load of NAC it has an efficient and quick absorption, with a predominant first pass metabolism both in the small intestine cells and the liver. This facilitates the incorporation of this amino acid into proteins, and the excretion of its metabolites. After this broad hepatic metabolism (with a minor participation of CYP450), the arrival of intact NAC molecules to plasma and tissues/organs afterward, is thus very limited (albeit it occurs in a small percentage). Its urinary excretion is around 22%–30%, with a half-life of 5.6 hours in adults, and 11 hours in neonates (Kelly 1998).

Acetylcysteine serves as a prodrug to L-cysteine. L-cysteine is a precursor to the biologic antioxidant glutathione, and the limiting nutrient. Hence, administration of NAC is considered a good replenishment strategy of the glutathione stores (GA eBusiness Services 2013).

NAC also prevents tissue injury for its participation as a superoxide radical scavenger. Recent studies have established a link between oxidative stress and neurocognitive deficits in psychosis. As a glutathione precursor with glutamatergic properties, the administration of NAC has shown efficacy on negative symptoms in patients with schizophrenia, and in global functioning in patients with bipolar disorder. According to Rapado–Castro and Dodd, NAC may have an impact on cognitive performance in psychosis, as a significant improvement in working memory was observed in the NAC-treated group compared with placebo (Rapado-Castro and Dodd 2016). NAC is an antioxidant with direct and indirect antioxidant actions used in the clinical setting. NAC exerts a significant protective role in liver injury following intestinal ischemia reperfusion (IIR), which seems to be independent of any intestinal protective effect that this amino acid could have per se (Kalimeris and Briassoulis 2016).

NAC has the possibility to influence the effects of nitric oxide (NO). Shimada et al. performed a hemodynamic study demonstrating that the increased left ventricular mass produced by myocardial inflammation tended to be reduced in rats treated with NAC in the context of experimentally induced myocardium inflammation of autoimmune origin (Shimada and Uzui 2015). Taken together, nNO synthetase seems to be responsible for the increase of total NOS activity in the brain of SHR. SMTC inhibited 86% and 70% of NAC-induced increase of total NOS activity in the brainstem and cerebellum, respectively. Thus, nNOS is responsible not only for strain differences but also for NAC-induced increase of total NOS activity in the brain (Pechanova et al. 2009).

Nakagawa and co-workers investigated possible influences of NAC (also as a precursor of glutathione) on joint tissue, particularly in the cartilage. They were interested in a potential protective role of NAC in articular chondrocytes against nitric oxide (NO)-induced apoptosis and a potential prevention of the cartilage destruction in an experimental model of osteoarthritis (OA) in rats. One of their observations was that NAC was able to inhibit NO-induced apoptosis of chondrocytes

through glutathione in vitro, and inhibits chondrocyte apoptosis and articular cartilage degeneration in vivo (Nakagawa et al. 2010).

NAC also plays important roles in respiratory/immune functions. Aliavi and Kurbanova analyzed 35 patients with community-acquired pneumonia. Studies of red blood cells and expired air condensate revealed significant nitric oxide metabolic disturbances in them. The established regularities in the balance change of nitric oxide metabolism in blood and expired air condensate at the height of the disease and positive changes during therapy including NAC suggest that nitric oxide plays an important role in the pathogenesis of community-acquired pneumonia (Aliavi and Kurbanova 2007). Other respiratory acute conditions are also susceptible to be treated complementarily with NAC, in relationship with an augmentation of glutathione levels after NAC supplementation in acute respiratory distress syndrome (Soltan-Sharifi et al. 2007).

One of the main and most investigated uses of NAC (even by conventional medicine) is the nephroprotection role. Intravenous and oral N-acetylcysteine may prevent contrast-medium–induced nephropathy with a dose-dependent effect in patients treated with primary angioplasty and may improve hospital outcome (Marenzi et al. 2006).

Glutathione precursor: NAC supplementation in diabetic patients is sufficient to increase intracellular GSH content in blood cells (Gamage et al. 2014). There are reports of a dose-dependent suppression of the insulin resistance phenomenon using some anti-oxidants, like NAC (Houstis et al. 2006).

The aim of this study was to investigate the effects of NAC on the levels of reactive oxygen species in sepsis. NAC treatment had beneficial effects on erythrocyte GSH, serum TNF-alpha, lung function, and kidney MDA levels in sepsis-induced rats. However, this beneficial effect was not confirmed as histopathological improvement (Gül et al. 2011). Oxidative stress and reduced brain levels of glutathione have been implicated in schizophrenia and bipolar disorder. N-acetylcysteine (NAC) is a precursor of glutathione and has additional effects on glutamate neurotransmission, neurogenesis, and inflammation. Glutathione depletion was reversed by NAC (1000 mg/kg) in saline-treated and amphetamine-treated (frontal cortex only) rats (Dean et al. 2011).

It has already been mentioned that the natural content of the thiol group confers NAC its antioxidant capacity. N-acetylcysteine is a natural thiol-containing antioxidant, a precursor for cysteine and glutathione, and a potential detoxifying agent for heavy metal ions (Sisombath and Jalilehvand 2015). Results show that Zn and NAC presented promising effects against the toxicity caused by HgCl2 (Oliveira et al. 2015). Cadmium (Cd) is known to cause severe damage to various organs including lung, liver, kidney, brain, and reproductive system. Several studies have reported the induction of oxidative stress pathways following Cd exposure. NAC can be used as a potential protective agent against Cd-induced testicular toxicity, especially with regard to oxidative stress-induced Leydig cell toxicity (Khanna et al. 2016). Cd is a well-known hepatotoxic environmental pollutant. Rat hepatocytes incubated with NAC and Cd simultaneously had significantly increased viability and decreased Cd-induced ROS generation. Our results suggested that Cd induces ROS generation that leads to oxidative stress. Moreover, NAC protects rat hepatocytes from cytotoxicity associated with Cd (Wang et al. 2014).

Stimulates Immune Function

NAC has also been hypothesized to exert beneficial effects through its modulation of glutamate and dopamine neurotransmission as well as its antioxidant properties.

Sulfur Amino Acids

Methionine, cysteine, homocysteine, and taurine are the four common sulfur-containing amino acids, but only the first two of these are actively incorporated into proteins. Cysteine, by its ability to form disulfide bonds, plays a crucial role in protein structure and in protein-folding pathways. Methionine metabolism begins with its activation to S-adenosylmethionine. Cysteine may be converted to such important products as glutathione and taurine (Brosnan and Brosnan 2006).

Antioxidant action due to the thiol groups of their molecules. Methionine residues constitute an important antioxidant defense mechanism. A variety of oxidants react readily with methionine to form methionine sulfoxide, and surface-exposed methionine residues create an extremely high concentration of reactant, available as an efficient oxidant scavenger (Levine et al. 1996, Di Buono et al. 2003, Moskovitz 2005).

5-Hydroxy tryptophan increases the production of serotonin in the nervous system (Jacobsen et al. 2016, Zhang and Zhao 2016). The amount of 5-HTP reaching the central nervous system (CNS) is affected by the extent to which 5-HTP is converted to serotonin in the periphery. This conversion is controlled by the enzyme amino acid decarboxylase, which, in the periphery, can be blocked by peripheral decarboxylase inhibitors (PDIs) such as carbidopa. Preclinical and clinical evidence for the efficacy of 5-HTP for depression is reviewed, with emphasis on double-blind, placebo-controlled (DB-PC) trials. Safety issues with 5-HTP are also reviewed, with emphasis on eosinophilia myalgia syndrome (EMS) and serotonin syndrome (Turner et al. 2006).

Branched Chain Amino Acids, Isoleucine, Leucine, Valine

AA mixture branched chain with direct stimulus to the nervous system and musculoskeletal system.

On the muscular mass, they exert an anabolic effect. Substantial evidence has been accumulated suggesting that branched-chain amino acid (BCAA) supplementation or BCAA-rich diets have a positive effect on the regulation of body weight, muscle protein synthesis, glucose homeostasis, the aging process, and extend healthspan (Bifari and Nisoli 2016).

Postinjury metabolism is characterized by breakdown of muscle protein as substrate for energy production and gluconeogenesis and by the resultant loss of lean body mass and weight loss. The results suggest that early nutritional support in the postoperative period will result in nitrogen equilibrium and that the infusion of the three BCAAs only in the postoperative state is as effective in preventing muscle catabolism as other more balanced amino acid solutions. In the postinjury state, balanced amino acid solutions rich in BCAA may prove beneficial (Freund et al. 1979).

Liver function optimization is another possible field for the use of BCAA supplements. These amino acids may also be useful in minimizing or reversing the catabolic state characteristic of patients with cirrhosis. A reduction of increased urinary 3-methylhistidine excretion by infusions of BCAAs in cirrhotic patients suggests an anticatabolic effect. These potential anticatabolic effects of BCAAs are interesting (Maddrey 1985).

L-Leucine

Optimizes hepatocyte function (Davuluri et al. 2016). Leucine supplementation has been reported to improve lipid metabolism. Chronic leucine supplementation reduced the body weight and improved the lipid profile of mice fed with a high-fat/cholesterol diet. This beneficial effect was ascribed to hepatic lipogenesis, adipocyte lipolysis, and white adipose tissue browning (Jiao et al. 2016) and neurons.

Besides its actions in lipid metabolism, leucine also promotes muscle mass gain, especially in the geriatric population (Murphy et al. 2016).

L-Carnitine

L-Carnitine has mitochondrial coenzyme functions (Valero 2014).

Useful in neurodegenerative diseases such as Alzheimer's disease (Lodeiro et al. 2014), review relevant experimental and clinical data on supplemental substances (i.e., curcuminoids, rosmarinic acid, resveratrol, acetyl-L-carnitine, and ω-3 (n-3) polyunsaturated fatty acids) that have demonstrated encouraging therapeutic effects on chronic diseases, such as Alzheimer's disease and neurodegeneration resulting from acute adverse events, such as traumatic brain injury (Gavrilova et al. 2011, Bigford and Del Rossi 2014).

Muscle degenerative diseases (La Guardia et al. 2013, D'Antona et al. 2014)

L-Carnitine is one of the usual orthomolecular supplements used in overweight patients, given some positive results regarding this indication. In a recent report, Pooyandjoo and colleagues

published the results of their meta-regression analysis of the duration of the amino acid consumption (Pooyandjoo et al. 2016). They observed that although there was a weight reduction associated with carnitine supplementation, its magnitude significantly decreased over time ($p = 0.002$). In conclusion, the authors state that receiving the carnitine resulted in weight loss, and consider that a meta-analysis of the different medications to aid weight management and non-pharmacotherapy measures should be considered for future research.

L-Taurine

At the central nervous system level, taurine improves GABAergic neurotransmission and has neuroprotective activity (Hovsepyan et al. 2015, Qiao et al. 2015, Wang et al. 2016, Zhu et al. 2016).

Taurine also improves liver functions (Wu et al. 2015) after having a chelating activity on transition metals (Zhang et al. 2014).

L-Arginine

L-Arginine is a conditionally essential amino acid that is involved in protein synthesis, the detoxification of ammonia, and its conversion to glucose as well as being catabolized to produce energy. In addition to these physiological functions, arginine has been purported to have ergogenic potential. Athletes have taken arginine for three main reasons: (1) its role in the secretion of endogenous growth hormone; (2) its involvement in the synthesis of creatine; and (3) its role in augmenting nitric oxide. These aspects of arginine supplementation will be discussed as well as a review of clinical investigations involving exercise performance and arginine ingestion (Campbell et al. 2004).

Stimulating growth hormone; acute resistance exercise and L-arginine have both been shown to independently elevate plasma growth hormone (GH) concentrations (Forbes et al. 2014).

Arginine is one of the most important cofactors involved in the production of nitric oxide.

Glycine

Structurally speaking, glycine is the simplest amino acid. It also modulates GABAergic neurotransmission: GABA and glycine are major inhibitory neurotransmitters in the CNS and act on receptors coupled to chloride channels (Ito 2016).

It is used mainly in neurodegenerative diseases. Glycine receptors (GlyRs) are ligand-gated chloride ion channels that mediate fast inhibitory neurotransmission in the spinal cord and the brainstem. There these receptors are mainly involved in motor control and pain perception in the adult nervous system (Avila et al. 2013).

Glycine can also act as a brain protector. In cerebral hypoxia-ischemia (HI) experimental models, glycine was able to protect neonatal rat brains against HI, in part by inhibiting TNFα-induced inflammation and gliosis. Hence, systemic glycine infusions may have clinical utility for the treatment of HI injury in human newborns. The results of Mori et al. (2017) suggest that acute Gly treatment reduces ethanol-induced oxidative stress and neuronal cell loss in SH-SY5Y cells and in the developing rat brain. Therefore, Gly may be considered a potential treatment in ethanol-intoxicated newborns and infants (Amin et al. 2016). Glycine stabilizes energetics of brain mitochondria under conditions of brain hypoxia in vivo modeled by ligation of the common carotid artery in rats. It is concluded that both in the model of hypoxia in vivo and during in vitro modeling of hypoxia in cortical slices and mitochondria, glycine acts as a protector inhibiting generation of reactive oxygen species in mitochondria and preventing energetic disturbances in brain mitochondria (Selin et al. 2012).

Beta-Alanine (B-Ala)

B-Ala is a naturally occurring amino acid (a non-essential amino acid) that is not stored in the body as muscle tissue. Rather, research has shown that B-alanine works by increasing the muscle content of an important compound—carnosine. In fact, the production of carnosine is limited by the availability of B-alanine. B-Ala has some interesting scientific evidence about its possible performance enhancement.

This amino acid has an indirect antioxidant function, since it increases intracellular levels of carnitine, which serves to control free radicals.

Buffer agent for pH variations. Isokinetic average power/repetition was significantly increased post B-Ala supplementation compared with placebo. Beta-alanine may benefit short-duration, high-intensity exercise performance (IJSM 2013).

BA supplementation, by improving intracellular pH control, improves muscle endurance in the elderly. This, we believe, could have importance in the prevention of falls, and the maintenance of health and independent living in elderly men and women (Stout et al. 2007, 2008, Artioli et al. 2010, Derave et al. 2010, AIS 2011).

L-Tryptophan

L-Tryptophan (Trp) is a large neutral amino acid essential to human metabolism because it is the metabolic precursor of serotonin (a neurotransmitter), melatonin (a neurohormone), and niacin (vitamin B3) (Attenburrow et al. 2003).

Tryptophan's primary mechanism of action is its role as the metabolic precursor of the neurotransmitter serotonin. Other neurotransmitters and central nervous system (CNS) chemicals, such as melatonin, dopamine, norepinephrine, and beta-endorphin, have also been shown to increase following oral administration of tryptophan (van Praag and Lemus 1986).

Other neurotransmitters and central nervous system (CNS) chemicals, such as melatonin, dopamine, norepinephrine, and beta-endorphin, have also been shown to increase following oral administration of tryptophan (Guilleminault et al. 1973, Chadwick et al. 1975, den Boer and Westenberg 1990).

Through its intravenous administration, Trp stimulates the secretion of hormones like prolactin and growth hormone (Winokur et al. 1986).

L-Ornithine

L-Ornithine (ORN) is another amino acid that is not included in protein structures. ORN has its main function in the urea cycle (1), along with two other amino acids (arginine and citrulline) and five enzymes. The objective of the urea cycle is to regulate the body concentrations of urea and ammonia. As nitrogen is closely related, the urea cycle can also be understood as a nitrogen detoxifying pathway. Also, the urea cycle may be one of the pacemakers for the availability of protein/amino acids at the hepatic level, and then ORN can have an indirect anabolic effect (Sivashanmugam 2016).

Releasing growth hormone activity: A change magnitude of serum growth hormone was significantly larger in the L-ornithine hydrochloride condition than in the placebo condition (Demura et al. 2010).

L-Lysine

Immune humoral function: L-Lysine is classified as an essential amino acid; meaning the human body cannot synthesize lysine on its own and thus must rely on adequate dietary intake to function properly. Lysine is rapidly transported into muscle tissue (Longenecker and Hause 1959), within 5–7 hours after ingestion (Uhe et al. 1992), and is more concentrated in the intracellular space of muscle tissue compared to other essential amino acids (Flodin 1997). This suggests that muscle may serve as a reservoir for free lysine in the body.

Lysine is the most strongly conserved of the essential amino acids. Lysine is converted to acetyl CoA, a critical component in carbohydrate metabolism and the production of energy. Lysine is also the precursor of the amino acid carnitine, which aids in transporting long-chain fatty acids into the mitochondria for energy production and other metabolic functions. Once lysine is bound to a polypeptide structure, biosynthesis of carnitine is initiated by methylation of one of lysine's amine groups (Broquist 1982). Clinical indications are herpes, osteoporosis, and angina pectoris, where research is published (AMR 2007).

L-Phenylalanine

Phenylalanine (PHE) is a biologically essential aromatic amino acid that acts as a precursor to tyrosine and the catecholamines (epinephrine, norepinephrine, dopamine, and tyramine). It acts also as precursor of melanin and as a constituent of many central nervous system neuropeptides (Wurtman and Caballero 1988).

From the therapeutic perspective, PHE crosses easily the blood–brain barrier (easier than any other amino acid), making it able to exert a direct influence on brain biochemistry.

Phenylethylamine (PEA) is a metabolic end-product of phenylalanine. PEA is further metabolized by monoamine oxidase type B to phenylacetic acid (PAA) (Yang and Neff 1973).

PEA is believed to have amphetamine-like properties, and urine levels have been found to be reduced in patients with depression. Using it as a diagnostic tool, Sabelli found significantly lower levels of PEA in plasma and urine in depressed subjects, compared with normal controls. Treatment with phenylalanine improved mood in 78% of depressed subjects (Sabelli et al. 1986).

There are some precautions to consider before administering PHE. This amino acid is counter indicated in phenylketonuric patients since they are not able to metabolize it and it would worsen their symptoms of phenylketonuria. In some patients with schizophrenia there have been reports of aggravation of tardive dyskinesia with the use of PHE.

As a supplement, PHE is one of the few amino acids that can be administered in any of its isomeric presentations, D, L or DL (as with methionine). Liver enzymes take on the conversion to the useful form, L-phenylalanine.

We have experience with the use IV of L-phenylalanine in concentrations of 0.5% (HeilPro DKN, Cali, Colombia), 1% (Farmacia Francesa, Buenos Aires, Argentina), and 2.5% (Farmacia Milenium, Buenos Aires, Argentina). The average doses range from 15 to 75 mg diluted in IV drip solution, along with other orthomolecular nutrients. Habitual associations include other amino acids with neurotropic functions, like L-tryptophan and/or methionine.

Choline

Choline is required to make the phospholipids phosphatidylcholine, lysophosphatidyicholine, choline plasmalogen, and sphingomyelin—essential components of all membranes. It is a precursor for the biosynthesis of the neurotransmitter acetylcholine. Several lines of evidence suggest that choline might be an essential nutrient for humans. In many other mammals, including the monkey and rat, choline deficiency results in liver and renal dysfunction (Zeisel 1988).

The demand for choline as a methyl donor is probably the major factor that determines how rapidly a diet deficient in choline will induce pathology. As expected, humans ingesting a choline-deficient diet for 3 weeks had diminished plasma choline and phosphatidylcholine concentrations. Choline deficiency of longer duration would have resulted in more prominent evidence of liver dysfunction (Zeisel et al. 1991).

In another publication Zeisel also noted that choline consumed by the mother has a role in cerebral development, with potential protection against future cognitive dysfunction in the offspring (Zeisel 2004).

Amino Acid Complexes to Specific Conditions

In our practice, we use some amino acid combinations through the intravenous route, to treat specific conditions:

- Nutri-Detox® (Biomolec, Ecuador)
  - Cysteine, Cystine and Methionine combined
- Nutri-Brain® (Biomolec, Ecuador)
  - Glycine 25 mg, L Aspartic acid 5 mg, L-Asparagine 15 mg, L-Glutamic acid 25 mg, L-Glutamine 25 mg, L-Lysine 25 mg, L-Methionine 25 mg, L-Phenylalanine 25 mg, L-Tryptophan 10 mg, N-Acetyl L-Tyrosine 5 mg

- Nutri-AA-Pool (Biomolec, Ecuador)
  - Vial containing a series of important amino acids for the maintenance of protein synthesis and related metabolic activities. Also covers the possible indications related to the specific amino acids contained in the formula:
    - Arginine 58 mg, Lysine 97 mg, Proline 84 mg, Cysteine 3 mg, Histidine 46 mg, Aspartic acid 27 mg, Alanine 73 mg, Methionine 47 mg, Valine 43 mg, Tryptophan 18 mg, Ornithine 26 mg, and Serine 25 mg

Vitamins

Vitamins are one of the oldest orthomolecular nutrients that have been found useful from the therapeutic point of view. Their discovery had its highest points in the first 4 decades of the twentieth century. At that time, diseases like beriberi, rickets, or pellagra were much more common than today, and doctors and scientists were able to determine their biochemical origin only after investigating specific nutritional deficiencies. Vitamins can be grossly divided in two main groups, according to their solubility: those that are soluble in water and those that are soluble in lipids.

Vitamins can be divided according to their hydrophobic or hydrophilic properties. Water-soluble vitamins include vitamin C and a heterogenous group of vitamins called the B complex vitamins, which are grouped together mostly because they can be found in the same foods. Ascorbic acid (vitamin C) was covered sufficiently in the section devoted to antioxidants. Fat-soluble vitamins include vitamins A, D, E, and K.

B Complex Vitamins

B complex vitamins comprise 12 water-soluble vitamins, but only 8 of these are considered essential for humans, since they cannot be synthetized de novo and thus must be ingested with the diet (or taken as supplements). Usually B complex vitamins are not stored for any length of time in the human organism, and so they must be replenished on a daily basis. The eight essential B vitamins have both names and their corresponding numbers: vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), vitamin 9 (folic acid), and vitamin B12 (cobalamin).

The B vitamins are widely required as coenzymes for different enzymes which are considered essential for many of the most determinant cell functions and metabolism. For example, B vitamins have an essential role on mitochondrial function maintenance. Energy production in the mitochondria can be compromised in the case of a maintained deficiency of any B vitamin.

B vitamins are found in whole unprocessed foods. Processed carbohydrates such as sugar and white flour tend to have lower B vitamins than their unprocessed counterparts. For this reason, it is required by law in many countries (including the United States, most European countries, Colombia and Argentina, among many others) that the B vitamins thiamine, riboflavin, niacin, and folic acid be added back to white flour after processing. Most of the times this practice is referred to as "Enriched Flour" on food labels. B vitamins are particularly concentrated in animal sources like some meats (e.g., in turkey, tuna, and liver) (Stipanuk 2006).

From the clinical point of view, B complex vitamins have had many different uses. Some of them have been more investigated than others. Neurodegenerative and psychiatric diseases, so as heart and cardiovascular diseases are among the most purported fields for its use.

They have been used as cofactors in some antioxidative protocols (e.g., the enzyme glutathione reductase is riboflavin-dependent, and it results essential to maintain intracellular concentrations of GSH). In our clinical practice we rarely use a single isolated nutrient, but rather a synergistic mix of them. B complex vitamins have also been utilized as pretreatment in some heavy metal chelation schemes.

Thiamine (Vitamin B1)

Thiamine is a vitamin B complex, also known as vitamin B1. Thiamine is a crucial nutrient in the correct functioning of the Krebs cycle for pyruvate decarboxylation (Frank et al. 2008). This

B complex vitamin also results essential for the oxidative decarboxylation of the multienzyme branched-chain ketoacid dehydrogenase complexes of the citric acid cycle (Depeint et al. 2006). The thiamine-dependent enzymes of the tricarboxylic acid (TCA) cycle are reduced following thiamine deficiency and in the brains of patients who died from multiple neurodegenerative disease. The results suggest that other TCA cycle enzymes should be measured in brains from patients that died from neurological disease in which thiamine-dependent enzymes are known to be reduced. The diminished activities of multiple TCA cycle enzymes may be important in our understanding of how metabolic lesions alter brain function in neurodegenerative disorders (Bubber et al. 2004). The observed increase in the excretion of pyruvate, lactate, 2-oxoglutarate (30-fold against control), and pentose phosphates (3-fold) with urine, depending on the degree of vitamin B1 deficiency, points to one of the essential mechanisms of cell metabolism stabilization under the given pathological condition (Gorbach et al. 1987).

Several groups of patients are at risk of thiamine deficiency, and the classic clinical picture of wet or dry beriberi is not always present, especially in cases of marginal deficiency (O'Keeffe et al. 1994).

Thiamine deficiency can be a cause of concern in groups with potentially low ingestion of this vitamin, like incarcerated prisoners, patients in drug rehabilitation, patients under prolonged parenteral nutrition, and institutionalized elders. Thiamine has also been found deficient in patients whose gastrointestinal absorption is compromised and/or the chronic nature of their disease suggests a possible increase in the output, like patients with hyperemesis gravidarum, anorexia nervosa, chronic kidney disease patients in hemodyalisis, oncologic disease, and AIDS (Hoffman 2011). Medications like furosemide and digoxine can hamper the pharmacokinetics and pharmacodynamics of thiamine, and thus the typical cardiologic patient receiving this type of drug for long periods of time can be at risk of deficiency (Zangen et al. 1998). Some regional risk of thiamine deficiency can be recognized in countries like Ireland or New Zealand, where it is not mandatory to supplement flour for human consumption with this vitamin (O'Keeffe et al. 1994).

Nevertheless, above all of these groups of thiamine deficient patients, alcoholics represent the most common and prototypical example for a variety of reasons. First, their main source of calories is alcohol, which also alters their judgment capacity and the proneness to consume a healthy and balanced diet. Second, ethanol by itself can diminish nutrient absorption at the gastrointestinal tract.

It is important to bear in mind that although adverse effects have been reported in the medical literature after the use of IV thiamine (Schiff 1941, Eisenstadt 1942, Leitner 1943, Stein and Morgenstern 1944, Reingold and Webb 1946, Assem 1973, Stephen et al. 1992, Leung et al. 1993, Morinville et al. 1998), this idiosyncratic reaction is exceedingly rare when compared to the hundreds of thousands of doses of IV thiamine that are given every year around the world.

Regarding this issue, Wrenn, Murphy, and Slovis carried out a prospective evaluation on the safety of thiamine hydrochloride (injected IV as a 100-mg bolus) (Wrenn et al. 1989). From a total of 1070 doses which had been given to 989 consecutive patients, they found an incidence of 0.093% for major reactions (one case of generalized pruritus) and 1.02% for minor reactions (11 cases of transient local irritation). Having a very low frequency of occurrence, the risk posed by this complication has been considered to be surpassed by the benefits of its supplementation in the case of thiamine deficiency and its consequences (mainly Wernicke encephalopathy).

In any case, as with any other potential adverse reaction with the use of any and all IV medication (Wrenn and Slovis 1992), staff should be prepared and trained in the proper treatment of allergic or adverse reactions.

Riboflavin (Vitamin B2)

Vitamin B2 plays an important role in enzymatic oxidoreduction systems. It also results in very important energy production via the respiratory chain.

In neurological diseases riboflavin has an antioxidant effect. The neuroprotective effects of riboflavin in motor disability of experimental autoimmune encephalomyelitis (EAE) as a model

of multiple sclerosis. Riboflavin is capable of suppressing the neurological disability mediated by BDNF and proinflammatory cytokine IL-6 (Petrovski et al. 2015, Shashi et al. 2015, Naghashpour et al. 2016).

According to Song and colleagues, eight phenolic compounds including: p-coumaric acid, vainillic acid, caffeic acid, chlorogenic acid, trolox, quercetin, curcumin, and resveratrol were treated with riboflavin (RF) photosensitization, and in vitro antioxidant capacities of the mixtures. RF photosensitization may be a useful method to enhance antioxidant properties like ferric ion reducing abilities of some selected phenolic compounds (Song et al. 2016).

Pyridoxine (Vitamin B6)

Pyridoxine or vitamin B6 is part of the vitamin B group, and its active form, pyridoxal 5-phosphate (PLP) serves as a coenzyme in many enzyme reactions in amino acid, glucose, and lipid metabolic pathways.

Pyridoxal 5-phosphate is involved in reactions catalyzed by the coenzyme aminotransferase. It is involved in many aspects of macronutrient metabolism, neurotransmitter synthesis, histamine synthesis, hemoglobin synthesis and function, and overall gene expression. This vitamin generally serves as a coenzyme (cofactor) for many reactions, including (but not limited to) decarboxylation, racemization, transamination, replacement, beta-group interconversion, and elimination (Combs 2008).

In relationship with carbohydrates' metabolism, vitamin B6 is required as coenzyme for glycogen phosphorylase, which is the enzyme necessary for glycogenolysis to occur. It can catalyze transamination reactions that are essential for providing amino acids as a substrate for gluconeogenesis.

Pyridoxal 5-phosphate aids in the synthesis of hemoglobin, by serving as a coenzyme for the enzyme 5-aminolevulinic acid synthase (ALA-S), ALA-S is the first enzyme involved in the biosynthesis of the group heme (Erskine et al. 2003, Ajioka et al. 2006). For an enhanced binding of the oxygen to hemoglobin, PLP binds to two sites of this protein.

PLP also plays important indirect roles in the nervous system, since it acts as cofactor in the biosynthesis of the most important neurotransmitters: serotonin, norepinephrine, epinephrine, dopamine, and gamma-aminobutyric acid (GABA). Regarding the synthesis of histamine, PLP is also involved. Keep in mind that these neurotransmitters dynamically regulate neural and emotional aspects like mood, attention, and vigilance. Its deficiency or imbalance can lead to a variety of clinical symptoms associated with depression (Muss et al. 2016). Many of the most commonly used conventional antidepressant drugs in psychiatry exert their pharmacological action due to their role in the serotonin metabolism and aim the amelioration of symptoms of depression and mood disorders. The serotonergic pathways rely on nutritional cofactors such as pyridoxine together with essential mineral and trace elements.

In diabetic experimental models (alloxan-induced), intramuscular (IM) injections of the vitamin complex containing: thiamine chloride (B1), riboflavin (B2), lipoic acid (N), calcium pantothenate (B5), pyridoxine hydrochloride (B6), folic acid (B9), and ascorbic acid (C) can reduce the blood glucose level in serum of rats (Petrov et al. 2014). It also helped stabilizing the activity of some enzymes of energy metabolism, lactate dehydrogenase, and pyruvate dehydrogenase complex.

Niacin, Niacinamide (Vitamin B3)

Niacin, also known as vitamin B3 and nicotinic acid, is an organic compound, essential in humans. In the first half of the twentieth century, vitamin B3 deficiency was a major public health issue. Between 1906 and 1940, more than 3 million Americans were affected by pellagra and it was associated with more than 100,000 deaths. Nowadays niacin deficiency is sometimes seen in developed and developing countries. It can make itself evident in poor socioeconomic conditions with poverty, malnutrition, and chronic alcoholism (Pitsavas et al. 2004). There is also the possibility of a borderline or mild deficiency. In this case, vitamin B3 deficiency has been shown to slow metabolism, and also cause decreased performance of the immune response and hamper the tolerance to colds.

In animal models and in vitro, niacin produces marked anti-inflammatory effects in a variety of tissues—including the brain, gastrointestinal tract, skin, and vascular tissue (Offermanns and Schwaninger 2015).

Niacin can also act as an antioxidant that promotes reducing function.

Neuroprotection Dietary intake and nutritional status of individuals are important factors affecting mental health and the development of psychiatric disorders. Lists of suggested nutritional components that may be beneficial for mental health are omega-3 fatty acids, phospholipids, cholesterol, niacin, folate, vitamin B6, and vitamin B12 (Lim et al. 2016). Niacin modulated the UPDRS scale, handwriting test, and quality of sleep parameters and showed the overall improvement without side effects (Wakade et al. 2015).

Cyanocobalamin (Vitamin B12)

Cyanocobalamin is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system, and the formation of red blood cells. It is one of eight B vitamins involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid and amino acid metabolism (Yamada 2013).

No fungi, plants, or animals (including humans) are capable of producing vitamin B12.

Vitamin B12 deficiency is most commonly caused by low intakes, but can also result from malabsorption, certain intestinal disorders, low presence of binding proteins, and use of certain medications. Vitamin B12 is rare from plant sources, so vegetarians are most likely to suffer from vitamin B12 deficiency. Infants are at a higher risk of vitamin B12 deficiency if they were born to vegetarian mothers. The elderly who have diets with limited meat or animal products are vulnerable populations as well (Killen and Brenninger 2013).

Vitamin B12 deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system (van der Put et al. 2001). At levels only slightly lower than normal, a range of symptoms such as fatigue, depression, and poor memory may be experienced (National Institutes of Health—Office of Dietary Supplements 2016). Vitamin B12 deficiency can also cause symptoms of mania and psychosis (Sethi et al. 2005).

Vitamin B12 is a co-substrate of various cell reactions involved in methylation synthesis of nucleic acid and neurotransmitters (Bottiglieri et al. 2000).

Vitamin B12 also influences brain function. In animals, fortification of foods with vitamin B12 and omega-3 fatty acids improves brain development (Rathod et al. 2016). Vitamin B12 along with folate, and sulfur amino acid content may be modifiable risk factors for structural brain changes that precede clinical dementia. The study by Hooshmand and colleagues suggests that the acceleration of the aging process in the brain has relationships with both vitamin B12 and total homocysteine concentrations (Hooshmand et al. 2016). Folate-dependent enzyme methionine synthase and vitamin B12 intake have been crucially related to brain development and function. Zhang and colleagues report previously unrecognized low vitamin B12 cerebral levels across the lifespan in relation with an adaptation to an increase in the antioxidant demand, while accelerated deficits of this nutrient due to GSH deficiency may be a contribution factor to neurodevelopmental and neuropsychiatric diseases (Zhang et al. 2016). Brain's functional organization in health and disease states can be evaluated through the resting state functional MRI (rsfMRI). Using rsfMRI can be a useful tool to evaluate the consequences in brain derived from vitamin B12 deficiency. This vitamin plays an essential role in brain networks associated with cognition control, a process exhibiting compromise in vitamin B12 deficiency (Gupta et al. 2016).

Folic Acid

Folic acid, another form of which is known as folate, is one of the B vitamins. It may be taken by mouth or by injection. It is also used to treat anemia caused by folic acid deficiency. It is used as a supplement by women to prevent neural tube defects (NTDs) developing during pregnancy

(Drugs.com 2016). The National Health and Nutrition Examination Survey (NHANES III 1988–1991) and the Continuing Survey of Food Intakes by Individuals (1994–1996 CSFII) indicated most adults did not consume adequate folate (Alaimo et al. 1994).

Many drugs interfere with the biosynthesis of folic acid. Among them are the dihydrofolate reductase inhibitors such as trimethoprim, pyrimethamine, and methotrexate; the sulfonamides (competitive inhibitors of 4-aminobenzoic acid in the reactions of dihydropteroate synthetase). Valproic acid, one of the most commonly prescribed anticonvulsants that is also used to treat certain psychological conditions, is a known inhibitor of folic acid. All the patients taking any of these medications will have to supplement folic acid in order to avoid a medication-related deficiency and the clinical consequences derived from it.

More than 50 countries require fortification of certain foods with folic acid as a measure to decrease the rate of NTDs in the population (Bailey 2009, Obeid 2012).

There is growing concern worldwide that prenatal high folic acid in the presence of low vitamin B12 causes epigenetic changes in the unborn predisposing them to metabolic syndromes, central adiposity, and adult diseases such as Type 2 diabetes (Yajnik and Deshmukh 2008).

Recently, long-term supplementation of folic acid has been associated with small reductions in the risk of stroke and cardiovascular disease (Li et al. 2016).

Research at the University of York and Hull York Medical School has found a link between depression and low levels of folate (Gilbody 2007), because it is necessary for the increase of the production of neurotransmitters.

Lipid-Soluble Vitamins

Lipid-soluble vitamins include vitamin A (retinol), vitamin D (1, 25 dihydroxycholecalciferol), vitamin E (tocopherols), and vitamin K (phytomenadione). Due to their solubility in fats, they are not routinely used in the everyday intravenous orthomolecular supplementation. To be injected, lipid soluble vitamins have to be prepared in special forms (like the micellar ones).

Minerals and Trace Elements

Minerals are inorganic nutrients required in small amounts for the correct functioning of cells and tissues. Depending on the mineral, its requirements can range from less than 1 to 2500 mg per day. Their presence is necessary for most of the normal life processes, but also to respond properly in disease states (Hays and Swenson 1985, Ozcan 2003).

As with other essential food nutrients, mineral in humans and other vertebrates has been thoroughly recognized as indispensable for many body structures and functions (Underwood 1971, Darby 1976).

Minerals can be found in different quantities in the human body. They can be classified as macro (major) or micro (trace) elements, according to the amount of a particular mineral in the organism. A third category is the ultra-trace elements. The macro-minerals are required in amounts greater than 100 mg/dL and the micro-minerals are required in amounts less than 100 mg/dL (Murray et al. 2000).

The macro-minerals or macro-elements include: calcium (Ca), phosphorus (P), potassium (K), sodium (Na), and magnesium (Mg). Meanwhile the micro-elements include: iron (Fe), copper (Cu), cobalt (Co), chloride (Cl), iodine (I), zinc (Zn), manganese (Mn), molybdenum (Mo), fluoride (F), chromium (Cr), selenium (Se), and sulfur (S) (Eruvbetine 2003).

Ultra trace elements such as boron (B), silicon (Si), arsenic (As), and Nickel (Ni) have been found present in human tissues and are believed to be essential. Evidence for requirements and essentialness of other minerals like cadmium (Cd), lead (Pb), tin (Tn), lithium (Li), and vanadium (Va) is weak (Albion Research Notes 1996).

Human beings must acquire minerals from external sources, in order to allow biochemical and metabolic processes to occur normally. The most common source is (and will/should always be) feeding, but supplementation has gained a place mostly due to micronutrient deficiencies. These

deficiencies lay upon many factors to develop, and currently represent a major public health problem. Traditionally it has been considered a problem affecting developing countries, with infants and pregnant women especially at risk, but the population from developed countries with highly westernized diets, and a significant load of antinutrient factors are also susceptible to have nutritional deficiencies (Batra and Seth 2002).

Infants need adequate micronutrients to maintain normal growth and development (Rush 2000).

When a trace element is deficient, a characteristic syndrome is produced which reflects the specific functions of the nutrient in the metabolism.

The trace elements are essential components of enzyme systems.

Simple or conditioned deficiencies of mineral elements therefore have profound effects on metabolism and tissue structure. To assess the dietary intake and adequacy of minerals, information needs to be collected on mineral element content of foods, diets, and water (Rao and Rao 1981, Simsek and Aykut 2007).

Mineral deficiencies or imbalances in soils and forages account partly for low animal production and reproductive problems. The uptake of minerals and other nutrients by plants is influenced by the concentration of these in soils, whose acidity and season of the year affect the availability of nutrients.

Plants use these minerals as structural components in carbohydrates and proteins; organic molecules in metabolism, such as magnesium in chlorophyll and phosphorus in ATP; enzyme activators like potassium, and for maintaining osmotic balance.

It has been reported to influence the mineral and trace element compositions of rice, wheat, oats, and barley, and these are mainly attributed to the altered soil conditions (Basargin and Peregudora 1969, Kavanek and Janicek 1969).

Uptake of copper, zinc, and manganese by plants is affected by the level of phosphate fertilizer (Mongia 1966, Baser and Deo 1967).

Cobalt, copper, iodine, and selenium deficiencies in the soil and flora in certain areas of the world have led to deficiencies of these minerals (Hays and Swenson 1985).

Antinutritional factors present in plants could also affect the absorption and availability of some minerals by humans and animals. Anti-nutritional factors reduce the nutrient utilization and/or food intake of plant foods (Osagie 1998).

Examples of antinutritional factors which could reduce the bioavailability of minerals are oxalates and phytates. Oxalic acid, like phytic acid, can bind some divalent metals such as calcium and magnesium thereby interfering with their metabolism. Phytic acid reduces the absorption of calcium from the gastrointestinal tract and consequently is implicated in the development of rickets when chicks are fed cereals such as sorghum (Blood and Radostits 1989).

Large amounts of calcium are required for the construction and maintenance of bone as well as for the normal function of nerves and muscles.

Phosphorus is an important constituent of adenosine triphosphate (ATP) as well as nucleic acid and essential for acid-base balance, bone and tooth formation.

Without iron, red blood cells cannot function properly. Iron is an important component of the cytochromes that function in the cellular respiration process.

Magnesium, copper, selenium, zinc, iron, manganese, and molybdenum are important co-factors found in the structure of certain enzymes and are indispensable in numerous biochemical pathways.

Vertebrates need iodine to make thyroid hormones.

Sodium, potassium, and chlorine are important in the maintenance of osmotic balance between cells and the interstitial fluid.

Magnesium is an important component of chlorophyll in plants.

The interactions between nutrition and diseases, nutrition and drug metabolism have been reported. The knowledge of the biochemistry of the mineral elements is also essential because individuals suffering from a chronic illness or taking medications that affect the body's use of specific nutrients need to be enlightened.

During two decades in our institution, we use macro- and micro-minerals in orthomolecular IV nutrition, with good results and excellent tolerance, as support in the treatment of many different pathologies, but at the same time as health support component, in sport practitioners and healthy people as functional boosters.

In the text below, we will address in detail the most important mineral elements we use in our daily practice.

Selenium

The trace mineral selenium (Se) is an essential nutrient of fundamental importance in human biology. As it is the case with many other mineral trace elements, Se performs its physiological functions not as an isolated ion, but in conjugation with other nutrients. For example, when it is bound to amino acids like cysteine in the form of selenocysteine, it plays important roles in many enzymatic reactions (Sunde 1997). Se is present as an integral component in more than 30 different selenoproteins (Mahima et al. 2012). Examples of Se-related enzymes are glutathione peroxidases, thioredoxin reductases, iodothyronine deiodinases, selenophosphate synthetase, among others (Arthur 2000, Rayman 2000). These enzymes are dependent on Se, with selenocysteine present at the active site. Rotruck and colleagues (Rotruck et al. 1973) had already suggested that selenium is a component of glutathione peroxidase more than 40 years ago.

Most of these selenoproteins wield fundamental roles both in general metabolic functions, for example, antioxidation in all the body systems and cells with glutathione reductases; organ-specific functions with influence on the whole system, for example, conversion of triiodothyronine (T_3) from its prohormone thyroxine (T_4) and regulation of its levels with thioredoxin reductases; and purely organ-specific functions, for example, potential protection of the developing sperm with spermatid selenoprotein 34 kDa (Rayman 2000). The detrimental consequences of Se deficiency in human and animal health can be easily understood after analyzing these enzymatic metabolic roles.

Se deficiency is recognized as a major health issue. By the beginning of the twentieth century it was estimated to affect from 0.5 to 1 billion people around the world (Combs 2001). Meanwhile, an even larger number of the world's population may be ingesting a lesser amount of selenium than the one required for the maintenance of optimal health (Haug et al. 2007). This deficiency has been identified in many parts of the world, like most of the European countries, China, and the South Island from New Zealand, just to provide some examples (Oldfield 2002, Rayman 2004). Volcanic regions for instance are noted for their low levels of Se in their soil. In many areas of Europe, aspects like the acidity of the soil, along with a higher soil complexity due to a high iron or aluminum content tend to reduce the uptake of Se by crops.

It should be mentioned that although there isn't any specific pathological condition in human beings associated exclusively to Se deficiency alone (Fordyce 2012), this mineral is nowadays considered essential and its deficiency has been implicated in a number of diseases (WHO 1996, Rayman 2012) affecting diverse organs and systems. Resembling a U-shaped dose/effect curve, the excessive intake of Se has also been linked to some diseases, known for centuries. Marco Polo and other chroniclers from antiquity described signs and symptoms compatible with what is recognized today as Se toxicity (selenosis) in pasture animals exposed to highly concentrated Se in forage grass or plants proceeding from soils later found to be excessive in Se (Fordyce 2012).

Human Se-deficiency diseases must be differentiated according to the severity of this deficiency. In some regions with extremely low intake of Se, particular clinical pictures may develop in severely depleted subjects. The two most iconic conditions derived from this extreme deficiency are (Reilly 1996, Fordyce 2012)

- Keshan disease, an endemic and potentially fatal dilated cardiomyopathy, whose name comes from an outbreak in Keshan County (northeast China) in 1935 but has been found in other regions of this country. There were several outbreaks during the rest of the twentieth century;

- Kashin-Beck disease, a deforming osteoarthropathy named after the Russian scientists who described it in the second half of the nineteenth century. It has been detected in several east countries (China, Siberia, North Korea, and possibly some parts of Africa).

These pathologies were first identified in areas of China where the soil is extremely low in selenium (Reilly 1996), and their incidence declined after compulsory Se supplementation (Reilly 1996, Rayman 2004), to the point that they are no longer considered public health problems in China. Nonetheless, in both cases other causative co-factors (dietary mycotoxins, chronic viral infection, iodine co-deficiency) besides Se severe deficiency are believed to play fundamental roles for the processes to develop (Rayman 2000).

Se has impact on several physiologic functions, including the balance in redox systems, the thyroid hormonal metabolism, and the immune system response, among others. Regarding the central role of the mineral in thyroid activity, Se is considered an essential micronutrient that is incorporated into iodothyronine deiodinases. These enzymes are directly involved in thyroid hormone metabolism (Köhrle 2015).

Se is a trace element that plays key roles in thyroid physiology, mediating in the conversion of T4 to its active form, T3. Se deficiency is associated with increased risk of thyroid disease. Some evidence suggests that Se supplementation may be beneficial in autoimmune thyroid disease (either hypo- or hyperthyroidism) (Negro et al. 2016). Se supplementation has been shown to decrease thyroid peroxidase antibodies (TPOAb) in autoimmune thyroiditis (van Zuuren 2013), although it is not completely clear yet if this decrease is protective or associated with less thyroid autoimmunity (Hegedüs et al. 2016).

Supplementation of (oral) Se has been considered quite safe, even after the long-term administration of 200 ug dosages in Se-deficient patients (Calissendorff et al. 2015) or 166 μg in Se-sufficient patients (Leo et al. 2017). Some mild to moderate adverse effects were reported in a small trial of chemoprevention for prostate cancer with a high-dose (1600 μg or 3200 μg), long-term (12 months in average) Se supplementation scheme was reported by Reid and colleagues (Reid et al. 2004). Most of these undesirable effects affected the skin and nails, and the authors emphasize that no serious adverse events occurred.

Se supplementation has been recommended by some authors in clinical situations with decreased antioxidant capacity, like hospitalization in the intensive care unit. Regarding this issue, there is still a great amount of debate over the utility of IV Se supplementation schemes in the critical patient. The recent publication of a critical review and meta-analysis by Manzanares and colleagues (2016) points out the lack of efficacy of Se as a monotherapy for the reduction of morbidity and/or mortality in the ICU.

Nonetheless there have also been reports of positive results with the simultaneous use of several antioxidants (Collier et al. 2008). The protocol published by Collier et al. consisted of the administration for 7 days of vitamin E (as alpha tocopherol, 1000 UI every 8 hours by naso or orogastric tube), vitamin C (as ascorbic acid, 1000 mg IV every 8 hours), and selenium (as selenious acid, 200 mcg IV daily in a 2-hour drip). Reductions in hospital mortality were statistically significant in this retrospective cohort study with 4294 trauma ICU patients (6.1% in the group of patients treated with antioxidants compared to 8.5% in the reference group of patients without the antioxidants; $P = 0.001$). This represented a 28% relative risk reduction in mortality.

The most complicated subgroup of the trauma patients (Trauma Revised Injury Severity Score [TRISS] 0.5) had a stronger reduction in the mortality rate. Other parameters (hospital/ICU length of stay, ventilator and ventilator-free days) did not change with the antioxidants scheme.

A later retrospective analysis of the trauma patients in the Collier study (Giladi et al. 2011) also revealed significant reductions in a variety of morbidity states associated with the critical patient. The group receiving the antioxidants had less respiratory failure rates (27.6% vs. 17.4%; $P = 0.001$), less abdominal wall complications (2.9% vs. 0.7%; $P = 0.01$), and less infections (both in the site of surgery [2.7% vs 1.3%; $P = 0.002$] and in the bloodstream originated in catheters [5.2% vs 4.9%; $P = 0.02$]). Other issues like renal failure and SIRS did not show significant differences between groups.

Traditionally Se has been linked to an antioxidant function, but it is important to note that it can also have a pro-oxidative role, depending on the compounds it incorporates into (Haygood et al. 2012).

Supplementation of Se in the clinical setting can be implemented through the oral and intravenous (IV) routes. As mentioned earlier in this chapter and in the same way it occurs with many other orthomolecular nutrients, each one of these routes has its own advantages and disadvantages. The oral route is safe, simple, and economically accessible, but needs weeks to months to achieve higher Se blood and plasmatic levels. As reported by Outzen et al., in the case of foods traditionally recognized as Se sources these levels did not raise so much as expected after the ingestion of 1 kg/week of fish and mussels for 26 weeks (~50 μg selenium/day) in a sample of healthy Danish men and women (Outzen et al. 2015).

Another potential oxidative stress rich situation where the use of Se has been considered potentially useful is malignant disease. Several tumor patients' populations have been found to have low Se serum levels in observational studies. This finding in cancer patients motivated further investigating supplemental oral Se to try to reduce the risk of developing malignant tumors. In this context, it is very important to consider that anticancer effect from Se was obtained from selenium-enriched yeast (SeEnY), but not from selenomethionine (SeMet) supplements. The NPC trial (Nutritional Prevention of Cancer trial) (Duffield-Lillico et al. 2003) was able to show a decrease in the prostate cancer incidence by 52%–65% with patients taking SeEnY, while the SELECT (Selenium and Vitamin E Cancer Prevention Trial) (Klein et al. 2011) patients did not achieve any benefit in prostate cancer risk reduction after 5.5 years taking different SeMet schemes (with or without vitamin E). The SELECT was ended prematurely due to lack of prevention in the antioxidant groups and, in fact, the vitamin E only group had a slight increase in the risk of developing prostate tumors in comparison to the placebo and other groups.

This phenomenon hasn't been clearly understood, while the information on Se biology is not yet complete and many questions remain unanswered about the cellular and genetic interactions of Se (Hatfield and Gladyshev 2009). Some have pointed to the very slight differences between the two forms of Se supplement. It is clear that both forms contain mainly selenomethionine, but SeEnY also contains little amounts of other sulfur compounds like gamma-glutamyl Se-methylselenocysteine and methylselenocysteine, which some have postulated as responsible for anticancer effects observed in the NPC trial. Apart from that, there are some discrete pro-oxidant properties of selenite, which is an Se species with potential contribution to ROS-mediated apoptosis. Malignant cells usually exist under mild oxidative conditions and many of them can be more vulnerable to oxidative stress than normal cells. There is some research toward the development of oncologic medications based on selenite that utilize oxidative damage as its main anticancer mechanism. These hypotheses were put to test in a recent trial that was able to demonstrate a different biochemical antioxidative profile derived from the use of SeEnY versus SeMet in a randomized trial with healthy volunteers (Richie et al. 2014).

In our orthomolecular experience, we use IV Se (as +4 selenite from HeilPro DKN, Cali, Colombia; oxide selenite from Farmacia Milenium, Farmacia Francesa, Buenos Aires, Argentina) in doses ranging from 60 to 120 μg added to other orthomolecular supplements, like high dose vitamin C and amino acids in the complementary treatment of malignant disease (as explained in the vitamin C section, every 4–6 days in average) or chronic infectious diseases (every 10–15 days on average). The treatment of acute infectious disease is another use we give to IV Se with high dose vitamin C drips (every 2–4 days for 2–5 infusions).

We've also used it in patients with autoimmune thyroid disease, but we tend to give preference to the oral route, long-term supplementation of Se in that situation. Another possibility we have put in practice is the combination of this permanent long-term oral Se supplementation dose with occasional Se IV drips (injected through IV drips along with multiple mineral preparations and amino acids).

Zinc (Zn)

Zinc is a micronutrient considered essential (since 1963 [Prasad 2013]) for the maintenance of health in humans and many animals. This trace element results in a wide range of organic functions

(Hambidge 2000). Some of these functions are related to cellular survival, proliferation, and development, even from the level of genetic expression (MacDonald 2000). Approximately 2 billion people around the world remain at risk of Zn deficiency, turning this into a public health issue which was underestimated for decades. Primary Zn deficiency syndromes may be due to diets poor in zinc (Hambidge 2000, Chatterjea and Rana 2012c).

Zn tissue contents vary depending on the organ (Chatterjea and Rana 2012a,b,c). It is high (70–86 mg/100 gm) in skin, and prostate. Zn is moderately concentrated (15–25 mg per 100 gm) in bones and teeth. Low Zn (2.3–5.5 mg/100 gm) can be found in most inner organs like kidneys, heart, pancreas, and spleen; also in muscles. The brain and the lungs have the lowest levels of tissue Zn (1.4–1.5 mg/100 gm).

There are cases in which the intake of Zn can be appropriate, but various conditions predispose to its inadequate handling or use by the organism. Secondary or conditioned zinc deficiency occurs in situations like malabsorption syndrome or total parenteral nutrition, many chronic diseases like sickle cell disease, diabetes, liver cirrhosis, chronic renal disease, several malignancies, and other chronic disorders (King and Cousins 2006). Some medications also interfere with adequate Zn storage and use, like in patients treated with ethambutol, penicillamine, and with some anticonvulsants.

Zn is found as a component of more than 300 enzymes and hormones, making it one of the most important trace elements (Riordan 1976). There are lots of metabolic reactions in which Zn is an indispensable co-factor. For example, it works on the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients (King and Cousins 2006). Zn is crucial for enzymes like alkaline phosphatase, carnosinase, lactic dehydrogenase, alcohol dehydrogenase, and both RNA and DNA polymerase, for example, while it influences the activity of others like thymidine kinase and ribonuclease (Soetan 2010, Chatterjea and Rana 2012c). Zn is the only metal with presence in all enzyme classes (Osredkar and Sustar 2011).

Once absorbed in the gastrointestinal tract, most of Zn contained in plasma is transported bound to albumin, but 10% of this mineral is transported by α2-macroglobulin (Chatterjea and Rana 2012a,b,c). At the intracellular level, Zn is the most abundant metal ion found in cytosol, vesicles, organelles, and in the nucleus (Fleet 2000).

Given that Zn influences so many enzymatic and metabolic processes in the human organism, its deficiency can be found to affect a broad diversity of organs and systems, including the integumentary, gastrointestinal, central nervous system, immune, skeletal, and reproductive systems.

One of the roles of Zn is as adjuvant in carbohydrate metabolism. In this context, Zn is required for the crystallization of insulin. Although the Zn concentration is low when compared to other tissues, one of the organs where Zn can be found readily available is the pancreas. Within the pancreatic cells, Zn is also a constituent of stored insulin (Chatterjea and Rana 2012c).

Zn plays a vital role in the maintenance of immune functions, including cellular (Beck et al. 1997) and humoral immunity. Zn deficiency increases the susceptibility to infection since it affects multiple aspects of innate and adaptive immunity (Prasad et al. 1997). From the diverse subpopulations of T helper cells, the most sensitive to Zn deficiency is T helper subset 1 (Th1), whose response is essential to mount an effective defense against intracellular antigens (e.g., viral infections). In this regard, cytokines like IL–2 (as responsible for promoting lymphocyte proliferation in general), and IFN–γ (as the responsible for promoting Th1 proliferation in particular) showed important affection after the implementation of 8–12 weeks of experimental Zn-restricted diet (3–5 mg/d) in healthy human volunteers (Beck et al. 1997). It is to note that evident serum Zn deficit only appeared after 20–24 weeks of the institution of this experimental diet, much later than the impairment of the type 1 response cytokines' compromise. Th1 cells are indeed very sensitive to Zn depletion, while their main counterpart Th2 cells do not exhibit impairment in Zn-deficient diets in humans (Prasad 2000). An additional consequence of the limited IFN–γ production is the diminished monocytes/macrophages expansion. This certainly establishes a vicious circle, considering that these antigen presenting cells (APCs) both produce this cytokine (along with other proinflammatory molecules) and depend on it in order to get activated and to proliferate. Several interesting reviews have been

published over the years covering the topic of the Zn role in immune function (Shankar and Prasad 1998, Maares and Haase 2016).

Immunosenescence is the progressive dysregulation of immune function capacity over the years, a condition especially noticeable in individuals after their sixth decade. The process's physiopathology is not fully understood yet, but factors like chronic infections through life (particularly cytomegalovirus infection), genetic predisposition to chronic low-grade inflammation (among others), and nutritional deficits have been postulated as predisposing elements to develop immunosenescence. Zn is one of the nutrients with most potential for the amelioration of age-dependent alterations on the immune system, along with other trace minerals like selenium, or vitamins like vitamin D and vitamin E. Recently Pae and Wu have provided a very complete review on this topic (Pae and Wu 2017), where they summarize the available intervention studies to date with Zn supplements in elderly patients. Besides playing a predominant supportive role in T-cell dependent immune response (in numbers and in function), Zn also induces augmentation of NK cell cytotoxicity and serves as a co-factor for thymulin, one of the thymus proteins declining with age. In Zn supplemented geriatric patients, additional immune achievements included an increase in delayed type hypersensitivity (DTH) response, and vaccination efficacy. The net result of this immune parameter enhancement was a reduction in morbimortality from infections in the Zn supplemented population (with doses ranging from 7 to 100 mg of Zn, and periods averaging several months). As with other indications, the authors emphasize that Zn supplements will have much more impact on the immune parameters in those elders with Zn deficiency, being less significant in those with normal Zn levels and healthy.

There are several infections (chronic and acute ones) in which Zn supplementation can be of potential benefit. For instance, Sharquie and Al-Nuaimy report on the successful local treatment of viral warts (especially the recalcitrant forms) with intralesional injection of 2% Zn sulfate (Sharquie and Al-Nuaimy 2002). Oral supplementation of Zn also proved effective in the treatment of this condition (Al-Gurairi et al. 2002).

Some recent publications (Maywald and Rink 2016, Rosenkranz et al. 2016) oblige us to consider also an immune tolerance induction role for Zn. From a general theoretical perspective, the immune system functioning is markedly complex: more frequently than not, a substance can have both immunopotentiating and immunomodulating behaviors. This will spin around the circumstances in which this substance acts (a nutrient, for instance). This could be the beginning of a possible role for Zn as an orthomolecular adjuvant measure in autoimmunity or transplantation tolerance induction, but the research is still young on this matter.

One of the subgroups of patients most expected to present a progressive deterioration of their immune function (including mucosal immunity/chronic diarrhea) is the one of those infected with HIV. In this case, Baum and colleagues performed a randomized controlled trial to evaluate oral long-term Zn supplementation (12–15 mg/day) as an adjuvant measure (Baum et al. 2010). They report a decrease in the likelihood of immunological failure and diarrhea in HIV+ patients with poor viral control. As with other essential nutrients, an increase in mortality and more advanced disease in HIV+ patients have been associated with persistently diminished Zn level in serum.

Diarrhea and enterocolitis have been areas of interest for the use of oral Zn supplements. The available evidence is not as strong as to recommend giving Zn to all patients with diarrhea, but it points to a beneficial effect on diarrhea in subjects belonging to populations with potential Zn deficiency. This has been observed mostly in developing countries with high rates of malnutrition and the usually associated Zn deficiency (Walker and Black 2010, Galvao et al. 2013). Some authors mention shorter diarrhea duration of 9%–23%, and a less severe disease in those children taking oral Zn when compared to control children with diarrhea but not taking the supplement (Black 1998).

The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) have recommended the use of Zn as part of the treatment of diarrhea since 2004 (WHO/UNICEF 2004), due to this positive influence in a disease with important mortality and morbidity around many areas of the world. Nonetheless, some authors from developed countries do not consider this recommendation necessary (Goldman 2013) in children who eat a regular diet, given their low

prevalence of Zn deficiency. The opinion on the issue is far from being uniform, even between the medical community in the same country (Giles 2013), considering that (from the nutritional point of view) rural populations even in developed countries like Canada are very different from urban populations.

Concerning cutaneous issues, Zn facilitates wound healing, and helps maintain normal growth rates, and normal skin hydration. Zn-dependent matrix metalloproteinases augment autodebridement and keratinocyte migration during wound repair (Lansdown et al. 2007).

In the nervous system, Zn has several important roles. It intervenes in senses like taste and smell, and its deficiency has been linked to the clinical presentation of these symptoms. In the elderly population, when combined with frailty, memory disturbances, and the heavy use of medication, hypogeusia and hyposmia related to Zn deficiency can also represent another burden factor (Pisano and Hilas 2016).

Zn also has an interesting role in depression. Its supplementation can help optimize treatment results and lead to gain control of depressive symptoms in patients who were previously not responding to classic antidepressant medications. It should be clarified that Zn cannot be considered an antidepressant substance by itself. On the other hand, to date the results of the clinical intervention trials still yield conflicting results (Sarris et al. 2016). Being an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor, Zn has a potential antidepressant-like activity in rodent tests/models of depression (Nowak et al. 2005). This trace mineral is also capable of inducing the gene expression of important neurotrophic factors like the brain derived neurotrophic factor (BDNF) (Szewczk et al. 2011).

The role of Zn in healthy aging is particularly important as it could help in the prevention of neoplastic cell growth. Zn is also involved in mitotic cell division, DNA and RNA repair (Tudor et al. 2005). It is involved in structural stabilization and activation of cytochrome P53 that appears to be an important component of the apoptotic process and also in activation of certain members of the caspase family of proteases (Dhawan and Chadha 2010), regulating the cell cycle.

As with many other orthomolecular supplements, like for example Se, N-acetylcysteine or vitamin C, Zn can also provide an antioxidative defense. From the conceptual point of view, the antioxidant mechanisms of Zn have been divided into two categories, depending on the duration of the Zn exposure (supplementation), whether it is acute or chronic. A detailed explanation of the mechanisms is provided by Powell in the review article about Zn antioxidant capacity (Powell 2000).

Diabetes mellitus is a chronic disease with a long list of complications, almost related entirely to the excess of oxidative stress. A role in the prevention of diabetes complications has been propounded recently by McCarty and DiNicolantonio for high dose Zn supplementation (McCarty and DiNicolantonio 2015). According to the authors, this action could be achieved not only due to the inherent capacity of this element to favorably influence the glycemic control in type 2 diabetics, and also to protect the pancreatic beta cells from oxidative stress thus reducing the risk for developing diabetes, but also due to the capacity of counteracting the copper effects through the induction of antioxidant protein metallothionein. Other measures reducing copper in experimental and clinical settings were able to reduce diabetic complications.

As any nutritional deficiency, Zn deficiency may arise from any alteration in one or more steps of the supply chain. Zn can be undersupplied, in cases of poor nutrition or anti-nutrient factors. But it could be ingested or supplemented in adequate amounts and not being properly absorbed. Even supposing a proper absorption, Zn could be handled deficiently and its transport in the body and/or its cell utilization could be impaired. Finally, Zn stores could be spent in a higher rate in most of the chronic diseases, being the issue an augmentation of its losses.

In some rare cases, Zn deficiency may result from a congenitally inherited defect of Zn absorption (deficiency of the Zn carrier protein ZIP4), called acrodermatitis enteropathica (AE). It is a severe Zn deficit syndrome, with an autosomal recessive genetic trait more common in families of Italian, Armenian, or Iranian origin. AE is usually lethal unless treated. It represents the most extreme of the consequences of Zn deficiency (Prasad 2013), with growth retardation, severe

diarrhea, ophthalmic damage, skin and teguments compromise (with baldness or hair loss and skin rash localized most often around the genitalia and mouth), and immune impairment with thymic hypoplasia and recurrent infections due to a variety of pathogenic bacteria but also due to opportunistic germs like candida sp.

Much more commonly seen in the clinical practice, the Zn deficiency is mild to moderate in its presentation. It is acquired secondarily from a variety of factors affecting dietary Zn intake, absorption, or loss. An excellent example of a patient with limitation in the replenishment of Zn levels after oral supplementation was published recently by Vick and colleagues (Vick et al. 2015). In this clinical case, it is thought that the patient's original suboptimal response to oral supplementation of Zn and the improvement after receiving IV Zn were related to the prior surgical history of alteration of the gastroduodenal anatomy and bypass of the absorptive capacity at the duodenum and jejunum.

One of the conditions associated with Zn deficiency due to a combination of digestive factors including classical malabsorption syndrome is the one derived from Crohn's disease (Solomons et al. 1977, McClain et al. 1980a). In these patients, Zn deficiency is also frequently caused by low intake, besides the poor absorption of this and many other nutrients (Sturniolo et al. 1980). To make things even more complex, Crohn's disease patients also present with an excess of Zn fecal losses (Wolman et al. 1979).

Some patients with extensive Crohn's disease may need IV nutrition, which should include the replenishment of Zn along with many other nutrients (Driscoll and Rosenberg 1978). Zn deficiency in Crohn's disease patients is not only derived from the complex intestinal luminal phenomena characterizing this condition. A group of 10 patients with Crohn's disease who needed IV nutrition were supplemented with IV Zn through a period of 5 weeks, and their serum and urinary Zn status was evaluated by Main and colleagues in the early 1980s (Main et al. 1982). Presurgical orthopedic patients and healthy volunteers were used as controls. According to the serum/urine Zn dynamics observed during the trial, the authors suggest that IV Zn supplementation does not present an efficient tissue transport. Also, they considered that Zn supplementation might be partially excreted as small molecular weight chelates into urine, and provide recommendations to enhance Zn utilization during IV nutrition in this complex context.

Long-term IV nutrition can be complicated by the development of Zn deficiency (McClain et al. 1980b) unless this mineral is adequately supplemented. Actually, the development of many of the previously recognized moderate to severe Zn deficiency related symptoms in patients receiving total parenteral nutrition (TPN) before the recognition of the essentiality of Zn was one of the main reasons to grant this trace element its essential status by the FDA and medical authorities (AMA 1979). This consideration becomes even more important when the patient is affected by an anabolic state, when Zn deficiency is more prevalent due to a higher expenditure of the nutrient.

This is also the case in some pathologic states. Zn deficiency is also associated with acute and chronic liver disease. Zinc supplementation may protect against toxin-induced liver damage and it has been used as a therapeutic measure for hepatic encephalopathy in patients refractory to standard treatment (Takuma et al. 2010). Another example of organic disease with augmentation of Zn stores is type II diabetes mellitus (Kinlaw et al. 1983), whose patients also develop Zn deficiency with time.

The clinical picture of Zn deficiency varies according to the degree of deficit. In a 2004 article (Yanagisawa 2004), Yanagisawa has skillfully and succinctly summarized the relationship between a given symptomatology and the degree of Zn deficiency in the patient.

- In minor Zn deficiency, the patient may present with symptoms like a subjective reduction in the sense of taste, signs like non-fat weight loss, and laboratory findings like a reduction in serum testosterone levels with or without alteration in the sperm counts.
- When the Zn deficiency is moderate, some of the aforementioned features will aggravate, like in the case of reproductive health with signs of delayed gonadal development. The structural system can be affected and there could be also growth impairment and

retardation. Skin abnormalities are also usual, with delayed wound healing. The nervous system will manifest moderate Zn deficiency with anorexia, somnolence, reduced dark adaptation, and in the sensorial sphere, symptoms like hypogeusia and hyposmia can be present at this stage.

- Continuing with the intensification of the Zn deficiency, severe depletion of this micronutrient will cause more serious skin conditions with bullous or pustular dermatitis or premature balding; abnormalities in the mental/emotional sphere (mainly depression); mucosal manifestations like (chronic) diarrhea; and eventually also affected immune response with recurrent infections.

The pathological situations leading to each one of these deficiency degrees are obviously different (Yanagisawa 2004). Slight micronutrient deficiencies (including Zn) tend to be of the consequence of marginal dietary ingestion of the implicated trace element and/or presence of anti-nutrient factors. To develop a moderate Zn deficiency, a deeper compromise of the nutrient intake is necessary, usually accompanied by unbalanced nutrition (Yanagisawa 2004, Murthy 2010); but it can happen also in pathologic states like malabsorption syndromes or chronic liver/kidney disease. Severe Zn deficiencies are almost exclusively associated with specific Zn metabolism detrimental conditions, like, for example, acrodermatitis enteropathica, or prolonged ethambutol/penicillamine treatments, or prolonged high-calorie parenteral therapy (Prasad 1976).

Even though in the clinical practice plasma or serum Zn level measurements are the most commonly used tool to evaluate a potential Zn deficiency, the real cellular Zn status could not necessarily be reflected by these levels (Osredkar and Sustar 2011). The homeodynamic mechanisms involved in controlling plasma levels of most nutrients are tight, and hence there can be differences with the extracellular matrix and intracellular status of such nutrients. This reflects a situation that can be seen commonly when assessing the patient's status of many trace elements. There is always the possibility of having a patient with clinical effects of Zn (or other micronutrient) deficiency without the presence of abnormal laboratory measurements.

Already in a 1979 study published by Aamodt and colleagues in the *American Journal of Clinical Nutrition* (Aamodt et al. 1979), they were able to demonstrate that similar metabolic patterns were observed regardless of whether Zn was administered intravenously or orally, suggesting that these patterns were not affected by the route of administration for the cases studied.

As with many other orthomolecular nutrients, Zn supplementation is still a matter of continuous investigation. Ideal therapeutic dosing to effectively ameliorate Zn deficiency is not clear yet, but maximum plasmatic levels below 30 mmol of zinc/L (approximately 200 mg) are considered safe to avoid any potential detrimental effect on the immune system (Ibs and Rink 2003). A U-shaped effect has been observed for Zn and the immune system function, where low as high doses are detrimental for its optimal state.

The repetitive administration of Zn in the absence of copper (Cu) supplementation may cause a (progressive) decrease in serum Cu levels (Plum et al. 2010, Osredkar and Sustar 2011). Zn has a high safety profile; in fact, most of its potential toxic effects have been associated with the potential induction of Cu deficiency (anemia, neutropenia, among others) (Plum et al. 2010). Periodic determination of serum copper as well as Zn serum levels are suggested as a tool to guide the Zn supplemental administration. Zn is eliminated via the intestine and kidneys. The possibility of Zn retention must be taken into consideration in patients with significant alteration in excretory routes (e.g., chronic renal disease). In these cases, an adjustment of the Zn supplementation dose could be necessary according to a lesser capacity of renal clearance of the ion.

Oral Zn overdose is possible, although it is rare, since it would be required to ingest very large amounts of the mineral to cause toxicity (Plum et al. 2010). A large oral dose of more than 30–40 g of Zn sulfate has been reported fatal. Severe Zn intoxication symptoms include: nausea, vomiting, dehydration, electrolyte imbalances, dizziness, abdominal pain, lethargy, and incoordination. The administration of a single IV dose of 1–2 mg zinc/kg body weight has been reported to have been

given to adult leukemic patients without any evident toxic manifestations. Normal plasma levels for zinc vary from approximately 88 to 112 mcg/100 mL. Plasma levels sufficient to produce symptoms of toxic manifestations in humans are not known. Calcium supplements could counteract Zn toxicity and may confer a protective effect.

In our clinic, we have experience with the use of zinc gluconate 1% solution (Farmacia Milenium, Buenos Aires, Argentina). The usual doses range from 20 to 80 mg, and it is added to the IV orthomolecular drip along with other nutrients according to the clinical picture and needs of the patient.

It is important to bear in mind that undiluted direct venous injections of Zn solutions should be avoided due to the potential risk of causing local irritation of the vessel (phlebitis), and there is a risk to induce a reflex augmentation of the Zn clearance at the renal level after a bolus injection of this mineral.

Copper (Cu)

Copper (Cu) is an essential trace element for humans and animals. It can be found in almost every cell of our organism, where Cu exists in the oxidized form. From the organs, the highest concentrations of copper are discovered in the brain and the liver; the central nervous system and the heart have high concentrations of copper as well (Gibson 2005). About 50% of total human body Cu content is stored in structural tissues, like bones and muscles (skeletal muscles alone contain about 25%). The other half of the Cu body content is distributed between the skin (15%), the bone marrow (15%), the brain (8%), and the liver (8%–15%).

Cu is a functional component of many essential enzymes, known as copper enzymes or cuproenzymes (Harris 1997). Some important examples are: cytochrome C oxidase, lysyl oxidase, feroxidase, 2-furoate-CoA dehydrogenase, amine oxidase, catechol oxidase, tyrosinase, dopamine beta-monooxygenase, D-galaktozo oxidase, D-hexozo oxidoreductase, indole 2,3-dioxygenase, L-ascorbatoxidase, nitratreductase, peptidylglycine monooxygenase, flavonol 2,4-dioxygenase, superoxide dismutase (SOD), PHM (peptidylglycine monooxygenase hydroxylation), and others. Some physiological functions are dependent on the presence of these enzymes in the organism (Rolff and Tuczek 2008).

Cu is absorbed mainly in the duodenum, but only about a third of Cu duodenal content coming from the diet can be absorbed. There are many factors limiting Cu absorption, like the presence of phytates, vitamins like ascorbic acid (but only in high amounts), and other minerals like zinc, molybdenum, cadmium, silver, and mercury (Chatterjea and Rana 2012).

The ability of copper to easily attach and accept electrons explains its importance in oxidative reduction processes and in disposing and removing free radicals from the organism (Uauy et al. 1998).

Changes in copper concentrations in body fluids and tissues are observed in different diseases and conditions. There are serious diseases, potentially caused by disorders in the metabolism of Cu in the organism. Low concentrations (abnormal) of Cu are found: Menkes syndrome (Kaler et al. 2008), Parkinson's disease, impaired intestinal resorption, parenteral nutrition (especially in the long term), excessive zinc supplementation, and diseases with protein loss (e.g., nephrotic syndrome, exudative enteropathy, and others). Meanwhile, other pathologic states exhibit increased Cu concentrations (Attri et al. 2006), like in pregnancy, cholestasis, malignant tumors and lymphomas, chronic degenerative liver disease (cirrhosis), increased ceruloplasmin—inflammation, myeloid leucosis, and Wilson's disease. Elevated circulating Cu concentration (hypercupremia) has been detected for decades in several situations, like acute and chronic infections and malignancies—leukemia, Hodgkin's disease, severe anemia hemochromatosis, myocardial infarction, hyperthyroidism, and so on (Lahey et al. 1953).

There is some controversy regarding the role of Cu in cardiovascular disease (Jones et al. 1997, Fox et al. 2000). While some scientists have suggested that elevated Cu levels can increase the risk of atherosclerosis (mainly through the oxidation of LDL), others mention how Cu deficiency (rather than Cu excess) would be associated with an increasing risk of cardiovascular

disease. More recent evidence (Grammer et al. 2014) points out that both ceruloplasmin and Cu serum level are independent markers of all cause and cardiovascular disease associated mortality. Approximately 3253 persons were evaluated by coronary artery disease (CAD) angiography and mortality both from all causes and from cardiovascular disease. After the proper removal of several confounding factors, the authors declared that the association was reduced but remained statistically significant.

When the dietary intake of copper was low, adverse changes have been observed in blood cholesterol, including increased total and LDL cholesterol and decreased HDL-cholesterol (Klevay 1998). Nonetheless, Jones et al. (1997) show that high dose Cu supplements taken for 4–6 weeks did not lead to clinically significant changes in cholesterol levels.

Copper-containing enzyme lysyl oxidase is required for the development (cross-linking) of collagen, which is a key element in the consolidation of the organic bone extracellular matrix. Osteoporosis occurs in children and adults with severe Cu deficiency, while in healthy adult men and women studies showed that the use of Cu supplements is able to induce significant increases in bone density (Baker et al. 1999). In elderly patients with hip fractures the serum levels of Cu were found to be significantly lower than these of controls (Conlan et al. 1990).

In patients with poor metabolic control, the reduction in plasma Cu concentration is less strong in women than in men with diabetes (Ruiz et al. 1998).

Cu was related to the manifestation of type 2 diabetes and should be applied in the treatment of diabetic patients (Tanaka et al. 2009).

Studies in children with chronic diarrhea investigated Zn and Cu status. The level of both trace elements in serum was reduced. The authors have found deficit of serum Cu in chronic diarrhea (Rodriques et al. 1985, Sachdev et al. 1990).

Serum levels of copper are higher in patients who use contraceptives or estrogens.

Copper might have influence on iron metabolism. As reported by Turgut et al. the Cu blood content in anemic patients showed increased serum concentrations of Cu in some cases. In turn, high levels of Cu induced a reduction in the absorption of iron and adversely affected hematological indices (Turgut et al. 2007).

It is known that copper plays an important role in the development and maintenance of immune system function. For instance, although not a common cause, neutropenia can be a clinical sign of copper deficiency in the human organism. Adverse effects of copper deficiency on immune function are most pronounced in infants (Failla and Hopkins 1998).

Extracellular matrix structural defects: On the other hand, copper is involved in numerous physiological and metabolic processes critical for the appropriate functioning of almost all tissues in the human body. In the skin, copper is involved in the synthesis and stabilization of extracellular matrix skin proteins and angiogenesis (Borkow 2014).

Manganese (Mn)

Manganese (Mn) is distributed in tissues throughout the whole body, but the highest concentrations are present in the liver, thyroid, pituitary, pancreas, kidneys, and the bone. At the intracellular level, Mn is largely located in the mitochondria. The total manganese content of an average 70 kg man is approximately 12–20 mg. A minimum intake of 2.5–7 mg per day meets human needs (Hegsted 1976).

Many nutrients from different families have synergistic interactions with Mn. These include minerals like potassium, zinc, magnesium, iron, phosphorus, and vitamins like A, E, B1, B3, B5, and B6.

It activates numerous enzymes—such as hydrolases, transferases, kinases, and decarboxylases—and is a constituent of some enzymes; the most well-known manganese metalloenzyme is pyruvate carboxylase, which catalyzes the conversion of pyruvate to oxalo-acetate. Arginase is involved in the conversion of the amino acid arginine to urea as well as mitochondrial superoxide dismutase (SOD) (Scrutton et al. 1966).

Manganese activates enzymes associated with fatty acid metabolism and protein synthesis. Mn results are important in the fatty and carbohydrate metabolism. It is also involved in some vitamin metabolism (Wilson et al. 1979).

Manganese is required for normal thyroid function and is involved in the formation of thyroxin. Studies have revealed low manganese levels in hypothyroid patients (Pfeiffer 1975).

Absorption or utilization of manganese may be impaired when levels of insulin, parathyroid hormone (PTH), and estrogen are elevated, affecting thyroid function (Watts 1989).

Many similarities exist among species in manganese deficiency; including skeletal abnormalities, postural defects, impaired growth, impaired reproductive function, and disturbances in lipid and carbohydrate metabolism. Manganese deficiency has been associated with symptoms like fatigue, growth pains in children, irregular menses, nervous system functions alterations, and joint issues (Underwood 1977).

Mn can play a complementary role as a supportive measure in the diabetic patients, due to the protection that Mn superoxide dismutase has over the oxidative DNA damage (Madsen-Bouterse et al. 2010).

Mn participates in chondroitin and proteoglycan synthesis. As these are two of the main components in cartilage, Mn can represent an indirect cofactor in the treatment of joint diseases and osteoporosis. In the wide sense, Mn is involved in the biosynthesis of mucopolysaccharides (main components of any extracellular matrix). A deficiency in Mn can then play a role in cartilaginous and collagen disorders. Skeletal abnormalities include chondrodystrophy, or retarded bone growth with bowing. Perosis or "slipped tendon" is a widely recognized condition in chickens and ducks deficient in Mn (Davies 1972, Underwood 1977).

Mn also intervenes in sexual hormones synthesis. Reproductive function in manganese deficient patients (both male and female) is characterized by defective ovulation, ovarian and testicular degeneration, and increased infant mortality.

Although it is not one of the main therapeutic measures, Mn can provide some benefits in the complementary treatment of allergic patients.

Other abnormalities thought to be related to manganese deficiency have been reported. Epileptics were found to have lowered blood concentrations of manganese, thus hypothesized to be a possible cause of cerebral dysrhythmia (Papavasiliov 1979).

Chromium

Chromium is a trace mineral essential for many animals, including humans. It is an element with multiple valences, being the most common form of chromium the trivalent one (Cr^{3+}). In the oral presentations, chromium can be consumed as a supplement in the form of chromium chloride, chromium nicotinate, chromium picolinate, or high-chromium yeast. One of the main reasons to justify the use of this mineral via intravenous (IV) infusion is the difficult absorption when taken orally (only 1%–10% according to the source used to obtain it, and according to the chemical form administered). Albeit severe deficiency of chromium can be considered somehow a rare condition, since there are plenty of dietary sources. On the other hand, reaching an effective replenishment time in patients with marginal chromium levels can take months when supplementing it orally.

Although the role of chromium in the glucose tolerance factor (GTF) was described as early as 1957, this did not necessarily translate into a higher use of this mineral in the clinical practice. Actually, as with many other micronutrients (for instance, zinc or selenium), the clinical importance of chromium for human health was unveiled only after periods of shortage in ICU patients maintained with total parenteral nutrition (TPN) (Freund et al. 1979, Brown et al. 1986). It was observed in this setting that after the addition of chromium to TPN the patients without prior history of blood sugar issues had a better glycemic control, and those with a history of diabetes mellitus required less hypoglycemic medications and/or achieved better values after having had difficulties with their metabolic status while in the ICU (Jeejeebhoy et al. 1977).

Chromium aids in the control of insulin resistance, thus helping the organism to keep appropriate blood sugar levels (Suksomboon et al. 2014). This turns it into a useful tool in the pathologic states of the carbohydrate metabolism, like diabetes and hypoglycemia (Paiva et al. 2015).

In another component of the metabolic performance, chromium also has important results for the correct lipid metabolism. It has been proposed that it favors a better body weight control, while helping in the reduction of blood levels of LDL cholesterol and triglycerides.

Diabetes and obesity are diseases characterized by their increasing incidence every year. When comparing with healthy subjects, the serum levels of chromium (Cr) are lowered in these two diseases. Several studies conducted in laboratory animals with experimentally induced diabetes demonstrated that supplementation with chromium ions (III) decreased glucose concentration in the blood, reduced the probability of atherosclerosis and heart attack, and lowered the levels of cholesterol and low density lipoprotein (LDL) (Lewicki et al. 2014).

Utilizing the powerful technology of nutrigenomics to identify the genes regulated by chromium supplementation may shed some light on the underlying mechanisms of chromium-gene interactions, and thus provide strategies to mitigate and prevent insulin-resistance-related disorders (Lau et al. 2008).

Chromium deficiency can be related to clinical manifestations like tiredness, diabetes or hypoglicaemia, loss of hunger, or LDL augmentation.

Electrolytes

Magnesium

Magnesium (Mg) is one of the main minerals with a potential therapeutic spectrum in the structural system. As such, it has been used extensively as a muscle relaxant, and for the treatment of diverse painful conditions, like neuralgia among others.

It can also act as a mitochondrial antioxidant, where it is conveniently associated to Coenzyme Q10 and/or alpha lipoic acid (ALA).

In diabetic patients, Mg can be associated with amino acids like alanine, and minerals like chromium, zinc, and B complex vitamins, in order to facilitate a better carbohydrate metabolism.

We have used Mg intravenously as magnesium chloride 20% solution (HeilPro DKN, Cali, Colombia; Farmacia Milenium, Farmacia Francesa, Buenos Aires, Argentina) or magnesium sulfate 10% solution (Farmacia Milenium, Farmacia Francesa, Buenos Aires, Argentina). It is added to multiple mineral preparations, along with amino acids and antioxidants like DMSO. Our main experience has revolved around the utility of Mg as an aid in pain control, with interesting symptomatic results in bone, muscles, and joint complaints.

Calcium

Improves muscle contraction
Premenstrual syndrome
Replacement of calcium after EDTA chelation

Multimineral Preparations

In our clinical practice, we have been working for many years with multimineral complexes as the base for many of the orthomolecular IV drips. This type of orthomolecular presentation provides an easy way to supply the patient both with macro minerals and trace minerals in fixed doses. It is common that individual minerals are added to the IV drip solution on an individual basis. Also, amino acids and antioxidants are added, in accordance with the intended therapeutic objectives for the particular patient. The most used multimineral complexes we use are

- Mineral Complex Nutri–Min 16 (Biomolec, Quito, Ecuador);
- MM-16 Forte (HeilProDKN, Cali, Colombia);

- MinTraz (OrthomoLab, Jamundí, Colombia)
- MetaBas (Farmacia Milenium, Buenos Aires, Argentina);
- Gluco-Mins (Cr, Zn, Mn) complex for use in glucose metabolism alterations

Precursors of Antioxidant Enzymes

Zn, Cu, Mn in Complexation with SOD

This product can be added to a 250–500 cc volume of saline solution weekly during 4–8 infusions, and after that every 15 days for 2 or 3 months.

Others

Chelating Agents

- Disodium EDTA
  - Chelating calcium, magnesium, lead, cadmium, chromium
- EDTA or sodium-calcium
  - Chelating lead, chromium cadmium
- Deferoxamine
  - Trivalent metal chelator
- Lipoic acid
  - Chelating lead, arsenic, mercury

D-Ribose

D-ribose is a pentose, which utilizes the oxidative pathway of phophate pentoses (PPP). After its IV injection, D-ribose is captured quickly by the cells and it is phosphorylated to ribose 5 phosphate. D-ribose plays a fundamental role in all ischemic processes, even those occurring at the muscular level. Animal studies corroborated a role of D-ribose in the myocardium recovery after ischemic stages, with a positive influence on contractile function of this muscle.

This pentose enhances quality of life in patients with reduced coronary blood flow and myocardium affection. D-ribose allows a better tolerance of the heart to ischemia in patients with coronary artery disease.

D-ribose also acts as a cofactor for ATP resynthesis. It can help in muscle fatigue derived from the loss of intracellular phosphate, therefore augmenting the exercise tolerance.

From a theoretical point of view, D-ribose can enhance insulin and hypoglicemic agents' activity. It is a complementary nutrient in the treatment of disglycemic patients, but it must be potentially avoided in patients with a marked tendency to hypoglycemia.

Inositol

Inositol is used by the body to form cell membranes, and it allows for the proper functioning of cells. Inositol assists in the transmission of nerve signals, and helps to transport lipids within the body. This will help to contract muscles more efficiently and will help to use body fat as fuel.

Inositol is a simple polyol precursor in important brain second messenger systems. Cerebrospinal fluid inositol has been reported to be decreased in depressive patients. Inositol optimizes muscle metabolism.

Procaine

Procaine is not an orthomolecular supplement per se, but we chose to make a short reference to it, since it is used routinely in many biological medicine practices around the world in the context of neural therapy according to Huneke (NTH). NTH is used along with orthomolecular supplements and some other therapeutic tools of biological medicine. Procaine acts as a cell membrane resting potential regulator with special emphasis on the restoration of the proper function of

the autonomic nervous system due to its role in disease (especially in the chronic ones) (Dosch 1984).

Apart from the neuratherapeutic use of procaine, many decades ago there were many reports by conventional colleagues about unexpected therapeutic effects after the application of local anesthetics. One interesting route is the IV procaine drip. Among other general regulatory actions, procaine is an inflammation modulator. Some bibliographic reports appeared in the 1940s by Graubard and colleagues. In the first one, the authors presented a method for the procaine IV drip and described 140 patients who received 608 intravenous procaine infusions for the management of pain in trauma and inflammation (Graubard et al. 1947). The next report was published the year after, including 448 cases with 1954 procaine infusions. In that one the authors wished to present further conclusions related to the safety of this method as a hospital procedure, and from the clinical point of view they mention that the average patient tolerated the procaine IV drip better when vitamin C is combined in solution (Graubard 1948). The same group continued working with IV procaine and producing reports about their advances (Graubard and Peterson 1949).

Considering the wide presence of the inflammatory process, the therapeutic action of local anesthetics holds a lot of promise for its clinical utility in many different areas and illnesses. Their noticeable effects on the inflammatory response and especially on several immune cells as promoters and effectors of the inflammatory response turns this class of drugs into modulating tools for a complex process. Some of the procaine and local anesthetics' effects have been evidenced mainly in polymorphonuclear granulocytes (PMNs), but macrophages and monocytes also exhibited changes. It is important to note that PMNs do not express Na channels, so the mechanisms of action must go beyond the classical one of the Na^+ channel blockade by local anesthetics (Krause et al. 1993).

From the point of view of biological medicine (and to some extent from conventional medicine [Cotran 1990, 1995]), the inflammatory cascade is essential for structural and functional repair of injured tissue. In some cases, however, inflammation can have a double-edged sword behavior. The uncontrolled and exaggerated generation of proinflammatory signals will lead invariably to a lesser or larger extent of tissue damage. This is what occurs in several disease states, and can be further aggravated due to tissue debris product from the same inflammatory process. Finding therapeutic tools that modulate rather than block the inflammatory response (e.g., procaine and local anesthetics) should eventually potentiate the favorable aspects of inflammation, while preventing excessive tissue damage. This postulate is in line with the principles of neural therapy.

Overactive inflammatory responses that destroy rather than protect are critical in the development of many perioperative disease states, such as postoperative pain, adult respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multiorgan failure. It accounts also as a big obstacle for the resolution in autoimmune diseases and many other chronic inflammatory conditions (e.g., COPD, neurodegenerative diseases, liver cirrhosis). Modulation of such responses is therefore a top priority from the point of view of any medical specialty that takes pride on practicing with a preventive orientation, like biological medicine.

Modern publications about the modulatory properties of local anesthetics in inflammatory diseases (Swanton and Shorten 2003, Pecher et al. 2004, Cassuto et al. 2006, Wright et al. 2008) echo the ones dating from more than a half century ago, but with a much broader view and fully equipped with many explanations about the molecular level interactions that these marvelous therapeutic agents have with effector proinflammatory cells.

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