



WFOT's Review on Evidence Based Ozone Therapy

(Version 1)

WFOT Scientific Advisory Committee 2015

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Preface

After being elected WFOT President in October 2014, one of my biggest concerns was to establish a public evidence based document on ozone therapy that collected and organized all the scientific information about this therapy.

Several books from Professor Velio Bocci, Dr. Silvia Menedez and Dr. Renate Viebhan have settled down the scientific basis. A recent book from Dr. Emma Borrelli, centered mainly on autohemotherapy, arrived to my attention a couple of months ago.

As president of the Spanish Society of Ozone Therapy - SEOT I had prepared during the past three years a document that was sent to the AEMPS (Spanish Agency of Drugs and Medical Devices) in order to start a regulation process of ozone therapy in Spain and in European Union. The authors of this text are acknowledged at the beginning of this document.

The first task I entrusted the WFOT Scientific Advisory Committee was that to develop a real evidence based text on Ozone Therapy, using this SEOT paper as a start point. Several modifications and improvements have been done to this document by all the members of the WFOT Committee in order to create a worldwide updated reference text. Dr. Lamberto Re as Chairman of the Committee has written the introduction section.

I hope we have contributed, almost in part, to a more comprehension of this therapy, allowing our colleagues to use it properly, following the most correct concepts.

*Prof. José Baeza Noci, M.D., Ph.D.
WFOT President*

Authors & Acknowledgements

To start from a solid base, we used the text prepared for the AEMPS (Spanish Agency of Drugs and Medical Devices) by the SEOT (Spanish Society of Ozone Therapy) in order to regulate the use of ozone in Spain. This document was prepared taking as a guide the book entitled "Ozone, a New Medical Drug" – Springer Publishing – New York, 2011, written by Professor Velio Bocci, from the University of Siena, Italy, with his explicit permission. We reached a consensus with the author on the main chapters so as to make a full scientific approach to ozone's medical use.

The content of such chapters have been reviewed, modified and expanded by:

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Introduction

In light of the growing interest about ozone therapy, it is our intention to update - both from a scientific and clinical point of view - its applications in the field of Human Medicine.

To our opinion, It is time that public opinion and health care professionals widen their horizons on ozone therapy and on its big potential at least as complementary or integrative support to conventional treatments.

Indeed, ozone therapy other than useful in numerous pathological conditions could be a powerful therapeutic resource to prevent the damages of aging and to improve many functions in our bodies.

Our scientific conviction that a molecule like ozone, i.e. a strong but very selective oxidant, could induce benefits in various ailments when used at proper doses was believed to be an unconventional theory. We are now very happy to note how this concept could finally gain a certain scientific credibility.

Anyway, avoiding emphasizing the anecdotal uses and looking to the wide clinical uses of the last decades, we think that a positive critical reappraisal concerning ozone therapy can't be further delayed.

It is also time for the dogma of the ozone toxicity to be finally clarified, recognizing its safety through full demonstrated safe applications.

Although ozone therapy is not exempt from side effects - mostly due to malpractice by poor training and / or ignorance - given its growing diffusion, these are negligible when compared to those deriving from other techniques and medications of universal acceptance.

We recognize that a puzzling skepticism still persists among many academic and official authorities, mainly due to prejudices and to the lack of more abundant pharmacological and controlled clinical studies. In our opinion, these facts do not justify the strong opposition to ozone therapy, but on the contrary should encourage the health authorities to help organizing such studies, taking into account that this therapy is not supported by the pharmaceutical industry and that it can contribute to improve the population health condition at much lower costs than other treatments.

It is true that, differently from any marketed drug acting with a precise and statistically defined mechanism following the mass-action law, ozone acts as a pro-drug activating a myriad of sub cellular events, many of them already elucidated in a significant part.

These actions are not easily associated to a particular clinical activity, and thus are very difficult to assay. Because of this, we do not have yet a precise methodological approach to evaluate and standardize the clinical efficacy of ozone therapy.

Nevertheless, once again we strongly think that this fact alone could not represent a valid reason to block any progress in the aim to look a little more beyond our current knowledge!

We can instead partially agree with the Health Authority regarding the difficulty to evaluate how every single clinicians using ozone therapy could prepare and administer its "drug" following the best good clinical practice. At the moment, due to the lack of official regulation, most of the ozone therapists are allowed to work with very scarce control of their scientific formation and of their therapeutic agent.

So far most of the clinical data regarding ozone treatment have been clearly defined from a scientific point of view only in the case of pain and disk hernia.

Despite these conditions, positive effects induced by adequate ozone doses are commonly

observed in patients suffering from rare or degenerative diseases. Nevertheless, the scarce knowledge of its therapeutic potential by most of the clinicians makes difficult or even impossible a wide cooperation among the various specialties in the aim to produce a statistical evidence of the clinical response to the ozone treatment.

Ozone, like other agents and unlike the common drugs that act on a specific receptor, induces a small and controlled stress to the whole cell when used at adequate doses. This, in turn, triggers a series of intracellular metabolic processes and promotes a myriad of activities stimulating many cellular mechanisms. Because of these reactions, the defense mechanisms of the cell are alerted and improve functionality, explaining in part the surprising therapeutic actions of this gas.

As it can be seen, it is not easy to fully describe the broad clinical applications of an agent so different from the common drugs!

This is the reason why WFOT decided to propose a revised document compiling the most relevant ozone therapy related literature scientifically based.

We hope that this document, which is primarily intended for health practitioners using ozone who want to refine their techniques and learn about the scientific bases that support the clinical use of this therapy, would be also useful to the health authorities as guideline and summary of the more recent research published worldwide.

Chapter 1

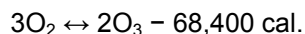
Physical-chemical properties of Ozone. Natural production of Ozone and its toxicity.

Ozone (in Greek, meaning it emanates an odor) is a natural and unstable molecule. The pure gas has a pale sky blue color and pungent smell. The molecule is made up of three atoms of oxygen (O₃) and its molecular weight, compared to that of the diatomic molecule of oxygen (32.00) is 48.00. Ozone's structure is cyclic, with a distance of 1.26 Å among the atoms, existing in different mesomeric states in dynamic equilibrium. It is useful for the physician to know that solubility (ml) in 100 ml of water (at 0°C) of both, ozone and oxygen, is 49.0 ml and 4.89 (ten-fold less), respectively. Consequently, ozone's great solubility in water allows immediate reaction with any soluble compounds or biomolecules present in biological fluids. Either traces of oxygen polymers (O₄) or ozone polymers (O₆ y O₉) can be generated; however, the idea that polymers/groups can have a therapeutic role is purely speculative (Cacace et al., 2001; Murai et al., 2003).

It is believed that during ozone generation, a trace of singlet oxygen (¹O₂) can be formed, but of negligible practical meaning.

Among oxidant agents, ozone is the third strongest after fluorine and persulfate, a fact which explains its high reactivity.

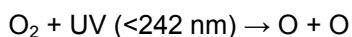
Ozone is formed by pure oxygen via an endothermic process requiring high voltage gradients between the electrodes of the Siemens' tube:



The reaction is reversible and, therefore, ozone is decomposed spontaneously, for which it cannot be stored. Also, half-life of ozone molecule depends on temperature thus at 20° C ozone concentration is half in 40 min., at 30° C in 25 min., while at -50° C is halved after three months.

In the stratosphere, approximately 22 km above the Earth's surface, there is an ozone layer that may reach a maximum concentration of 10 ppmv (parts per million-volume). Maintaining the ozone layer is very important for it absorbs most of the ultraviolet (UV) radiation (<290 nm) emitted from the sun. UV rays include UVA band (316-400 nm) responsible for suntan, and UVB and UVC bands (from 100 up to 315 nm), which are far more mutagenic and responsible for speeding up skin aging and carcinogenesis, as it has been recently demonstrated by a ongoing increase of carcinomas and melanomas.

Nature has been provident because, thanks to cyanobacteria, as soon as oxygen concentration started to increase in the Earth's atmosphere about 2.3 billion years ago, UV solar emission catalyzed ozone production (Chapman mechanism), which then could control UV radiation and protect the biological systems on Earth:



The protective ozone layer in the stratosphere is rather constant, as consequence of a dynamic equilibrium between the formation reaction and natural dissociation of ozone. This equilibrium has been subverted in the last century, due to a progressive increase of pollutants, mainly nitrogen oxides (NO_x) and chlorine derived from chlorofluorocarbons (CFCs) used in refrigerant fluids, incautiously dispersed in the environment. One single chlorine atom, via a catalytic reaction mechanism, discovered by Molina and Rowland (1974), can destroy thousands of ozone molecules before ozone is transported back to the troposphere.

Once again, chaotic human activities (industrial processes, vehicular traffic, etc.) have led to environmental damage by pollution of air in the troposphere, extending 8-17 km from the Earth's surface. Excessive anthropogenic emissions of nitrogen monoxide (NO), and the dioxide variant (NO₂), of carbon monoxide (CO), of methane (CH₄), sulfuric acid and other acid compounds have enhanced the almost unbearable increase of ozone concentration up to 0.3 µg/l or over. In large metropolis, ozone mixed with other substances form the photochemical smog: this has become the main toxicant for lungs, eyes, nose, and, to a lesser extent, the skin; it is particularly damaging for the respiratory mucosa since it does not have enough neutralizing substances against this harmful acid mixture. Undoubtedly, respiratory tract lining fluids (RTLFS), which can only amount to 20-40 ml dispersed as an aqueous film layer over alveolar space of about 70 m², becomes null without difficulty by this mixture of strong oxidants. Particularly, children, asthmatic and other bronchopulmonary patients are at risk and ozone "toxicomania" through respiratory route is well justified (Devlin et al., 1991; Aris et al., 1993; Broeckaert et al., 1999; Jerrett et al., 2009). Indeed, ozone toxicity brought up at street level has contributed to support the dogma that ozone is always toxic. Then, we may ask ourselves: why can ozone be used as therapeutic agent? Toxicologists and Sanitary Authorities are aware of this problem, which is clearly not only due to ozone and not supposed to convey the idea that ozone is "always toxic". Research in human activated leukocytes producing ozone in specific circumstances (Babior et al., 2003; Nieva and Wentworth, 2004) may be significant in understanding how useful it can be in physiologic and pathologic situations.

There are other three known gaseous molecules, namely, CO, NO and H₂S (Moncada, 1992; Verma et al., 1993; Pannen et al., 1998; Nakao et al., 2009a, b), which, like ozone, at physiologic doses may behave surprisingly as essential effectors but become toxic at high concentrations. Basically, the valid concept for any molecule is that the proper dose makes the difference between a therapeutic or toxic agent.

Therefore, for the safety of patients and health professionals, the environmental concentration of ozone must be controlled so as not to exceed an established threshold. The World Health Organization (WHO) allows working for 8 h when ozone concentration is 0.06 ppm, being perceived, well in advance, as a strong smell of ozone (0.01 ppm ~ 0.000002 µg/ml). This is advantageous as it timely warns us of the gas leakage. Needless to say we must not trust our nose because our olfactory receptors become tolerant and, in any case, air in clinics should be controlled concerning the ozone level.

Unfortunately, the fact that ozone concentrations are reported in ppmv as well as in µg/ml in USA and Europe, respectively, leads to confusion. Conversion is the following:

$$467 \text{ ppmv} = 1.0 \text{ } \mu\text{g/ml} \text{ or } 1.0 \text{ mg/l} \text{ or } 1.0 \text{ g/m}^3$$

$$1000 \text{ ppmv} = 2.1 \text{ } \mu\text{g/ml} \text{ or } 2.1 \text{ mg/l} \text{ or } 2.1 \text{ g/m}^3$$

$$1 \text{ ppmv} = 0.0021 \text{ } \mu\text{g/ml} \text{ or } 0.0021 \text{ mg/l} \text{ or } 0.0021 \text{ g/m}^3$$

Conclusions.

Ozone is a natural, very reactive and gaseous molecule, produced by an electric discharge and/or UV radiation, alone or with NO_x. Notably, even activated leukocytes generate ozone *in vivo*. It can be protective or harmful depending on its concentration and location. At present, a broad consensus has been reached for the use of ozone in industrial applications and water disinfection, though its medical use remains controversial since many physician-scientists are still skeptical about ozone and are not interest in learning or understanding its usefulness.

Chapter 2

Medical Ozone Generation.

Medical ozone must be generated using medical oxygen with an atoxic generator, in which all materials in contact with ozone must be inert to it, reliable and provide accurate and reproducible measurements of ozone concentrations (1-80 µg/ml) through an adequate device. Medical ozone is a mixture of ozone in oxygen, within the range of approximately 0.5 to 5 % of ozone concentration. Total dose of ozone is equivalent to the gas volume (ml) multiplied by the ozone concentration (µg/ml). In the European Union, ozone generators are considered as sanitary products with II-b qualification and must be registered in the notified entity of reference for the manufacturer. For different medical applications, the physician must know the optimal ozone doses, which will be dealt with in Chapter 9.

Chapter 3

Ozonated water and oil.

Ozonation of bi-distilled water and vegetable oils is carried out by bubbling a gas mixture ($O_2 - O_3$) in them. In the case of water, about 5 minutes will be enough for 2 or 3 liters, while for 100 grams of vegetable oil, several hours could be needed if medical ozone therapy equipment were used. We must take into account that many ozonides composed in vegetable oils are of an explosive character thus entailing a potential danger; subsequently, it is not advisable that unskilled people should perform this procedure. This is why ozonated oil is produced basically in semi-industrial laboratories, following safety measures and with the appropriate personnel.

Air must not be used to produce medical ozone for it can cause generation of toxic nitrogen compounds. Ozone concentration in pure water, due to solubilization of ozone, corresponds to about 25% of ozone concentration in the gas used, at room temperature, which is enough for optimal disinfection. One gram of oil can absorb more than 160 mg of ozone. While ozonated water is effective over one day if kept refrigerated, the oil remains stable for 2 years if kept cold. Both act as potent disinfectants and speed up healing by stimulating cell proliferation. Once the medical community acknowledges their efficacy, both, ozonated water and oil, could become essential tools in chronic wound care units. Currently, in European pharmacies there are products such as Azexin – ozonated sun flower oil – registered in EMEA as a sanitary product with indication for treating skin ulcers.

The problems in disinfecting drinking water and preventing nosocomial infections are now of primary importance because their cure is critical for many people's life or death. Compared with chlorine, ozone's versatility and efficacy remain unknown. Due to chlorine's unsatisfactory organoleptic characteristics, it is being gradually replaced by ozone, partly because of WHO recommendations in this regard. Ozone as drinking water disinfectant is stronger than chlorine and able to inactivate human pathogens as, for example, 63 different bacteria (Salmonella, Shigella, Vibrio, Campylobacter jejuni, Yersinia enterocolitica, Legionella, etc.), diverse varieties of yeasts and up to 13 pathogenic fungi (Alternaria, Monilinia, Rhizopus, etc.). More recently, due to groundwater contamination by fecal matter, the disinfection issue has become even more complex since encysted protozoa, such as *Giardia lamblia*, or cysts of *Cryptosporidium parvum* and helminth eggs (*Ascaris suum* y *Ascaris lumbricoides*), require of prolonged contact with ozone than bacteria and viruses. Each year, *Cryptosporidium* causes disease outbreaks that can be life-threatening for elderly patients or very ill ones (AIDS).

Another aspect in preventing outbreaks of intestinal infections is to possibly use ozone as antimicrobial agent in direct contact with food and fruits. On June 26, 2001, the Food and

Drug Administration (FDA) officially approved the use of ozone in gaseous and aqueous phases, as antimicrobial agent for the treatment, storage and processing of food (Rice, 2001). We must underscore that, besides disinfecting drinking water, the use of ozone can improve the organoleptic characteristics. In fact, it improves clotting and flocculation, oxidizes components of a bad taste and smell (as well as iron and manganese), enhances extraction of particles in filters through granular activated carbon. Efficacy of ozone has been validated by over 3000 municipal water treatment plants throughout the world (including Spain).

Chapter 4

Medical Ozone pharmacology and toxicity.

This is one of the key chapters, for we consider that if the physician is knowledgeable about how ozone acts with fluids and corporeal cells, may accomplish useful therapeutic outcomes. Ozone administration brings about certain biochemical reactions in the patient, and this is an essential part within the process.

Ozone, triatomic oxygen, synthesized in the stratosphere, protects us from excessive UV radiation, and can be produced accurately by a medical generator; however, it is up to us to use it as a drug or not. Ozone is one of the most powerful oxidants: the third on the chemical scale, and we must learn how to use it. On that ground, this chapter is aimed at defining its therapeutic coefficient or, to put it simply, to distinguish the therapeutic dose from the toxic one.

In spite of oxygen representing the greatest part (95-99%) of the mixture of medical ozone, it has a non-significant role over ozonated blood parameters since, *in vitro* conditions, the process of oxygen exchange with hemoglobin is very slow and, in plasma, only less than 1% of oxygen in blood is transported.

While we can only survive thanks to oxygen, this gas poses a long-term negative effect because cellular respiration originates reactive oxygen species (ROS), among others, hydroxyl radical (OH•), being one of the most destructive radical compounds to enzymes, and DNA. Halliwell (1994) estimated that, even at rest, man produces approximately 5g of superoxide anion ($O_2^{\cdot-}$) which is the parent of several radical molecules. Superoxide anion is physiologically produced by mitochondria, from Complex I and II (Kowaltowski et al., 2009), but other ROS, like hydrogen peroxide, hypochlorous acid and nitric oxide are continuously generated by several oxidases and myeloperoxidases, which in traces play a key defensive role against pathogens. On the other hand, most people know that ageing and metabolic disorders (atherosclerosis, diabetes, cellular degeneration) can worsen due to excessive ROS production and we can only prevent their damaging effects to a degree. Ironically, even partial deprivation of oxygen (hypoxia), observed in ischemic vascular diseases, represents a cause for death by limb ischemia, myocardial and cerebral infarction. Also, hypoxia enhances neoplastic metastasis afterward leading toward death.

The positive feature of ozone therapy, compared to other therapies based on philosophic postulates or non-verifiable hypotheses, is that it can be demonstrated by objective scientific researches with standardized biochemical, pharmacologic and clinical methods. It has been unfortunate for several decades that empiricism and lack of basic studies have delayed understanding the mechanisms of action. A lot of prejudice and inconsistent dogma that "ozone is always toxic" are responsible for the strong opposition of conventional medicine to use ozone therapy when it was part of its therapeutic repository up to the 40's.

Today, our duty is to try to demonstrate schematically that ozone follows perfectly the physical, chemical, physiologic and pharmacologic notions; and besides, activities modulating cellular functions are well-known.

First of all, ozone, as any other gas, readily dissolves in the water either of the plasma (the liquid part of blood), or into the extracellular fluids, or into the thin layer of water covering

the skin, and, specifically, in the mucosa of respiratory tract, throat, vagina, etc. At normal temperature and atmospheric pressure, due to high solubility and relative pressure-dependant, ozone dissolves in the organism's water, but unlike oxygen, DOES NOT ESTABLISH AN EQUILIBRIUM with the remaining ozone in gaseous phase. This is consequence of the high ozone affinity for carbon-carbon double bonds. Being a powerful oxidizing agent, it REACTS IMMEDIATELY with certain biomolecules present in biologic fluids, preferably, polyunsaturated fatty acids (PUFAs), bound to albumin and present in the great majority of lipids and phospholipids, as well as with antioxidants (Table 4.2), proteins and carbohydrates, etc. Indeed, phospholipids and cholesterol present in cell membranes and/or lipid-proteins are protected by antioxidants and albumin molecules rich in PUFAs (Bocci and Di Paolo, 2009, Travagli et al., 2010b).

Ozone reaction with so many molecules implies several basic processes occurring at the same time. Most part is consumed in a reaction of "unsaturated fatty acid addition to carbon-carbon double bonds", known as "Criegee Reaction", being one of nature's most rapid molecular chemical reactions (velocities of millions of moles/l per second) and very well depicted. This reaction, whose first product is denominated "primary ozonide", in hydrophilic physiologic conditions, with abundant water present, produces the breakage and immediate reorganization of its fragments, producing basically, as final result in presence of abundant water (as in the case of physiologic environment), aldehydes and a particular α -hydroxy-hydroperoxide of different structures depending on the initial fatty acids (Figure 4.1).

It is important to highlight that this particular α -hydroxy-hydroperoxide, in the terminal carbon of the lipid chain, and with an OH group in it, has a much less oxidant character than classic peroxides and, unlike the latter, do not generally yield free radicals. It may decompose in small proportion in hydrogen peroxide and the corresponding aldehyde with which establishes equilibrium.

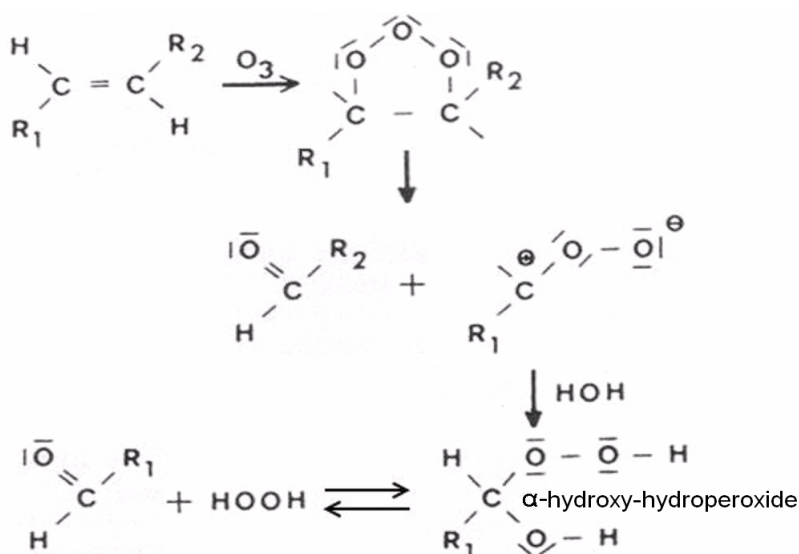


Fig. 4.1.

Part of primary ozonides can also bring about, to a lesser extent, a parallel reaction with direct formation of aldehydes and hydrogen peroxide (Figure 4.2).

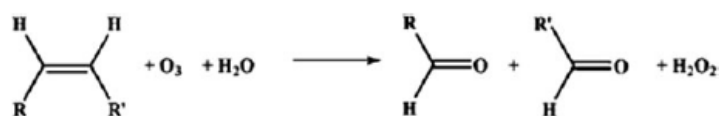


Fig. 4.2.

Because these reactions are molecule to molecule, they end rapidly with exhaustion of ozone supply. Thus, the oxidative stress produced can be well-controlled. This a crucial difference from the commonly known in biochemistry "LIPID PEROXIDATION" reaction, which preferably occurs by radical way (even faster); once started, it can spread very rapidly and extensively as well as oxidize a great number of lipid molecules and many other types of molecules in a non-controlled way.

These ozone reactions, completed in seconds, with a "specific" ozone dosage, only generate a "specific" quantity of α -hydroxy-hydroperoxides, aldehydes and hydrogen peroxide, similar as those recognized as LIPID PEROXIDATION PRODUCTS (LOPs).

Bocci (2002) has measured in plasma samples the production of both, LOPs and hydrogen peroxide after adding ozone (Fig. 4.3). However, measurement of hydrogen peroxide (H_2O_2) in full blood is very complicated, because it is quickly tampered by erythrocytes, so no trace of it is found. Fortunately, some studies (Bocci et al, 1993b; Shinriki et al., 1998) have confirmed a decrease in the GSH cytoplasmic content of the erythrocytes in the ozonized blood, supporting the fact that they capture the hydrogen peroxide that is generated by ozone (Fig. 4.4). This decrease is fully recovered after 20-30 minutes thanks to the generation of new GSH inside the erythrocytes.

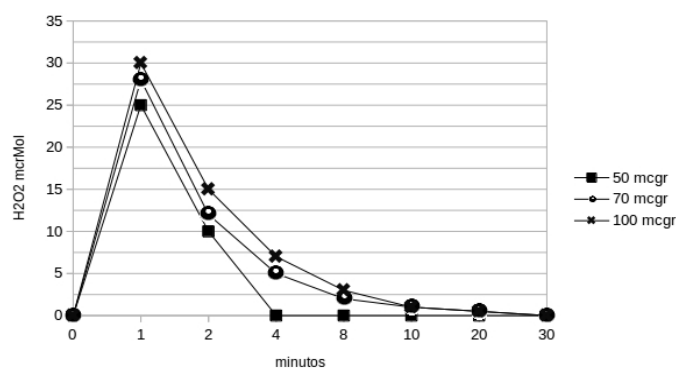


Fig. 4.3. Hydrogen peroxide produced by different ozone concentrations in plasma samples is neutralized by plasma antioxidant substances in a few minutes (Bocci, 2002).

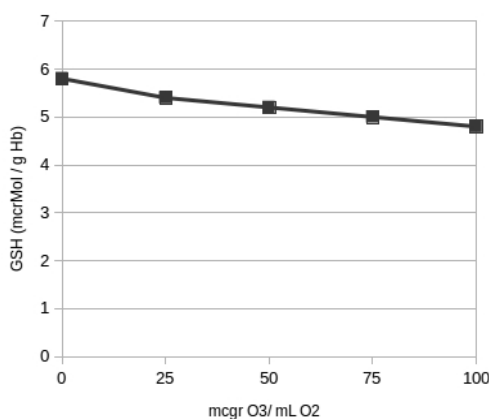


Fig. 4.4. After one minute of mixing ozone in full blood, there is a low decrease of erythrocyte's GSH that has a great affinity to H_2O_2 . At 100 $\mu\text{g}/\text{mL}$ the decrease is only a 17%. This decrease is recovered in less than 30 minutes. (Shirinki et al., 1998)

Small part of the ozone dosage is also consumed, inevitably, in the oxidization of other antioxidant substances present, such as ascorbic acid and uric acids, sulphhydryl (SH-) groups of GSH, proteins and glycoproteins in plasmatic water which usually recycle to their reduced form very fast. The amount of these antioxidant substances is different from one tissue to another and justifies the different ranges of ozone dosage according to the way of

administration (Table 4.1).

Table 4.1 Empirically-determined ozone doses and antioxidant capacities of body fluids and tissues (modified from Bocci et al. 2003)

Body fluids and tissues	Antioxidant capacity	Composition	Total antioxidant status	Ozone concentration (µg/mL)	Gas (O2-O3) Volume (mL)	Response
Plasma	High	See table 4.2	1,28-1,83 mM	-	-	-
Total blood	Very high	See table 4.2 See table 7.1	+++++	15-80	100-225	Therapeutic
BALF*	Very low	See table 7.1	+	None	-	Toxic
Skin(local) Skin(sauna)	Low	Non-enzymatic proteins, lipids, enzymes	++	5-80 0,1-0,9	Flux Diluted with air	Therapeutic
Subcutis	Moderate	Similar to plasma	++	2-20	1-100	Therapeutic
Colo-rectal mucosa y fluids	Low	Mucus, lipids, glycocalix, Non-enzymatic, Proteins, Enzymes	++	5-35	50-350	Therapeutic
Tooth	Low	Bacteria, proteins	?	4	100 in 10 seconds	Therapeutic
Nucleus pulposus	Moderate	Proteoglycans, collagen type I, II y IV	++	25-35	2-5	Therapeutic
Intraforaminal fluid	Moderate	Similar to plasma	++	30	15-20	Therapeutic
Epidural space	Low	Similar to plasma	+	10-20	20	Therapeutic
CSF**	Very low	Similar to plasma but very diluted	+	None	-	Toxic
Muscular fluid	Moderate	Similar to plasma	++	10-30	15-30	Therapeutic
Synovial fluid	Moderate	Similar to plasma	++	10-30	1-20	Therapeutic

* BALF: Bronchial associated lining fluid
** CSF: Cerebro-spinal fluid

Unlike the effects referred in studies about ozone toxicity through respiratory pathway and over the lung tissues (Pryor et al., 1995), where the natural antioxidant systems are practically absent by any of the rest of therapeutic administration methods, abundance of these natural antioxidant systems neutralize rapidly the “transient” slight oxidative stress accompanying therapeutic ozone administration.

The scheme (Fig. 4.5) has been illustrated to represent how ozone dissolved in organic water reacts simultaneously with hydrosoluble antioxidants and lipids bound to albumins. Likewise, it shows how ozone, at therapeutic concentrations, cannot reach the phospholipid bilayer constituting the erythrocyte membrane shielded by albumin molecules. It seems obvious that artificial experiments performed with erythrocytes washed with saline solution and very high ozone doses have demonstrated damages in the cellular membranes thus leading to a wrong belief that ozone is cytotoxic.

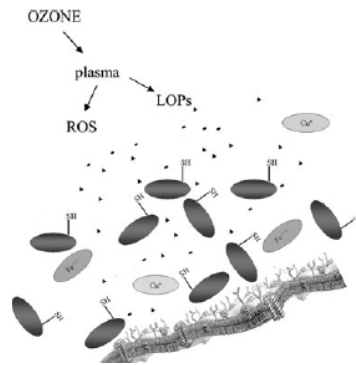


Fig. 4.5. The scheme (Bocci, 2011) helps to imagine the multiplicity of the substrate reacting with ozone dissolved in plasmatic water. Small circles, triangles and squares symbolize the hydrosoluble antioxidants present in 100 ml of human blood (uric acid 4,5 mg/dl, ascorbic acid 1,5 mg/dl, glucose 80 mg/dl, etc.). Large albumin molecules (4000 mg/dl) exposing -SH groups form a cloud over the cellular membrane and protect it. Molecules, such as transferrin and ceruloplasmin bound to Fe³⁺ and Cu⁺, prevent formation of OH⁻. Exogenous addition of 4-8 mg of ozone in 100 ml of blood is transitory and controlled by antioxidants. In contrast, endogenous ROS production is continuous and can only be controlled by enzymatic intra-cellular antioxidants.

4.1 Hydrogen peroxide and LOPS as ozone biological messengers.

Consequently, it should be clear that some of the ozone dose is neutralized by the antioxidants present in plasma and only reaction with PUFA is responsible for biologic and therapeutic effects. This should clarify why a very low ozone dose may be ineffective or equivalent to placebo. For blood, in people with a standard antioxidant status (TAS) (see table 4.1), concentrations under 15 µg/mL are completely tampered by plasma antioxidants and produce no LOPs or hydrogen peroxide (Fig. 4.6). Moreover, after human blood ozonation, the antioxidant capacity measured in plasma decreases not exceeding 30% after approximately 5 minutes, but returns to normal values during the next 15 minutes, thanks to rapid reduction of oxidized antioxidants with intervention of erythrocytes (Bocci et al., 1998b; Bocci and Aldinucci, 2006). This outcome emphasizes that even a high ozone dosage (16,000 µg. for 200 ml. of venous blood) never surpasses plasma antioxidant capacity, not causing any injury to the blood cells.

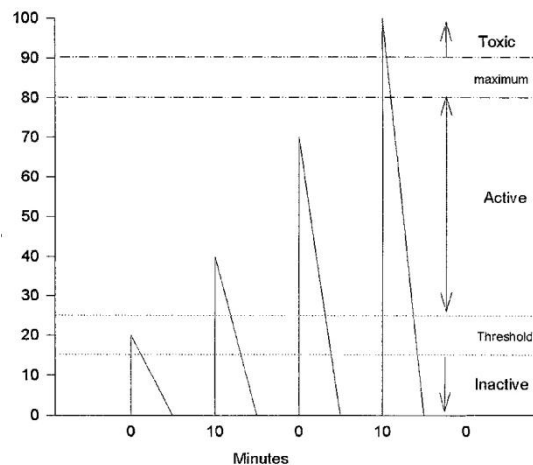


Fig. 4.6. Schema taken from Bocci's book 2002, showing the therapeutic range of ozone for blood. Concentrations between 15 to 25 µg/mL cannot be effective according patient's TAS. Concentrations under 15 µg/mL are not effective even in patients with very low TAS.

ROS include several radicals, such as superoxide anion (O₂^{-•}), nitrogen monoxide (NO[•]), peroxynitrite (O=NOO⁻), the aforementioned hydroxyl radicals and other components, such as hydrogen peroxide and hypochlorous acid (HClO). All the components are potentially cytotoxic (Fridovich, 1995; Pullar et al., 2000; Hooper et al., 2000); fortunately, they have a very

short half-life (usually, a fraction of second) and either plasma or cells have antioxidants able to neutralize them if their concentrations do not exceed the antioxidant capacity. This concept emphasizes the reason why ozone dosage must be accurate and well-calibrated against the antioxidant capacity of the blood to, consequently, trigger useful reactions without causing any damage.

LOPs generated after ozonation of a great variety of PUFAs are heterogeneous and, in short, represented by a variety of α -hydroxy-hydroperoxides in end carbon (R-OOHOH) and a complex mixture of aldehydes of low molecular weight, mainly malondialdehyde (MDA) and alkenals, among which is 4-hydroxy-2,3 trans-nonenal (4-HNE) considered by many as key element in cellular signal transduction (Awasthi, Y. et.al., 2004). Chemistry and biochemistry of these compounds is depicted masterly by the Esterbauer group (1991). If one thinks about the chemical wealth and heterogeneity of lipids, glycolipids and phospholipids in plasma, it turns out difficult to imagine that many potent compounds, potentially harmful, can be generated by lipids reacting with small quantities of ozone used in ozone therapy.

Considering that we must control (using accurate ozone concentrations related to blood volume and antioxidant capacity) the quantity of LOPs, we can achieve unthinkable multiple biologic effects with a single medication. Indeed, a great expert in antioxidants, Prof. Lester E. Packer of the University of California at Berkeley, has written that the hypothesis that a low ozone dose can bring about a number of useful antioxidant responses for the organism is rather reasonable and in line with current thoughts.

The following scheme underlines this crucial point and the sequence of events eventually generating the therapeutic effects: ROS are only produced over a short period of time, a few seconds, and they produce EARLY biologic effects in blood, while LOPs, produced simultaneously, have a longer half-life and reach the vascular system as well as practically all organs where the LATE effects are produced. (Figure 4.7).

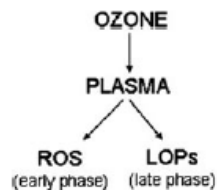


Fig. 4.7. The scheme (Bocci, 2002) tries to demonstrate that ozone dissolved in plasmatic water reacts immediately with certain biomolecules and disappears. Compounds generated during reaction (ROS and LOPs) represent the "ozone messengers" and are responsible for biologic and therapeutic effects.

How can we reconcile the production of toxic compounds with the idea that these compounds exert important biological and therapeutic effects?

Let us first examine the behavior and pharmacodynamics of hydrogen peroxide, which in practical terms is the most important ROS. As soon as ozone dissolves in plasma water and reacts with PUFAs, the concentration of hydrogen peroxide starts to increase but, just as rapidly, decreases because the molecule diffuses quickly into erythrocytes, leukocytes and platelets, activating several biochemical pathways.

The increase in intracellular concentration of hydrogen peroxide is not toxic for the cell, because at the same time, a reduction to water takes place in plasma and in intracellular water, thanks to the presence of potent antioxidant enzymes, such as catalase, glutathione-peroxidase (GSH-Px) and free reduced glutathione, as we have already commented (GSH). Perhaps for a few seconds, the chemical gradient between plasma and the intracellular concentration of hydrogen peroxide has been estimated to range from 1 to 4–5 μ M equivalent to about 10% of plasma concentration, which avoids any toxicity (Antunes and Cadenas, 2000; Stone and Collins, 2002; Stone and Yang, 2006; Forman, 2008). The transitory presence of hydrogen peroxide in the cytoplasm acts as one of the ozone chemical messengers and its level is critical: it must be above certain thresholds to be effective but not too high to become noxious. In

studies, performed with human blood (200 ml) exposed to ozone concentrations ranging from 20 to 80 µg/ml (corresponding to total doses between 4 000 and 16 000 µg of O₃ per session using 200 ml of blood, that is, 4 to 16 mg per session), the process of hydrogen peroxide generation, diffusion and reduction was always transitory (Bocci et al., 1993^{a, b}, 1998^{a, b}) also, Halliwell et al. (2000^{a, b}) considers that the molecule is really physiologic in the body.

Corroborating this idea, hydrogen peroxide is recognized as an intracellular signaling molecule capable of activating tyrosine kinase, which phosphorylates transcription factor (Nuclear Factor Kappa-B, NFκB), allowing synthesis of a certain number of different proteins (Baeuerle and Henkel, 1994; Barnes and Karin, 1997). Basically, hydrogen peroxide works oxidizing cysteines (Rhee et al., 2000); and several authors have determined that it acts over mononuclear blood cells (Bocci and Paulesu, 1990; Bocci et al., 1993b, 1998a; Reth, 2002), platelets (Bocci et al., 1999^a), over endothelial cells (Valacchi and Bocci, 2000) and over erythrocytes (Bocci, 2002).

ROS going into erythrocytes are almost immediately reduced, as we have seen (hydrogen peroxide to water and lipid peroxides to hydroperoxides) by GSH. Huge mass of erythrocytes can easily exhaust hydrogen peroxide and, in 10-15 min., recycle the oxidized antioxidants recovering them in their reduced form (Mendiratta et al., 1998^{a, b}). Meanwhile, glutathione reductase (GSH-Rd) uses reduced nicotinamide adenine dinucleotide phosphate (NADPH); this coenzyme serves as donor of electrons for several biochemical reactions) allows to recycle oxidized glutathione (GSSG) to its original level of GSH, oxidized NADP is reduced after activation through pentose phosphate pathway, of which glucose-6-phosphate dehydrogenase (G-6PD) is a key enzyme. Thus, glycolysis is speeded up by constant increase of ATP levels. Moreover, erythrocyte reinfusion, over a time period improves oxygen delivery to ischemic tissues because of a shift to the right of the oxygen-hemoglobin dissociation curve due to a slight decrease of intracellular pH (Bohr effect) and/or to an increase of 2,3-diphosphoglycerate (2,3-DPG) levels (Figure 4.8).

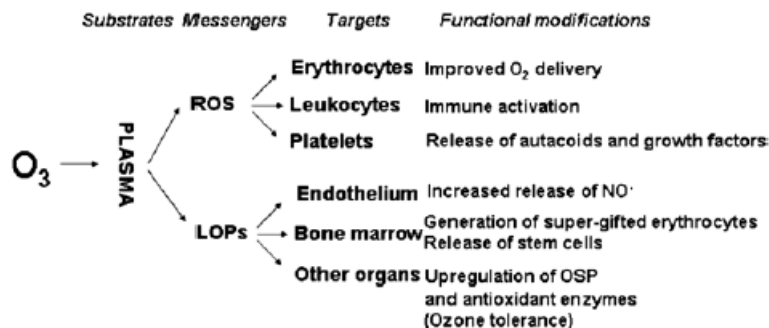


Fig.4.8. A summary of biologic effects obtained during human blood exposure to oxygen-ozone, ex vivo and while/after reinfusion in the donor (Bocci 2011)

There is an extensive literature on cytotoxicity of LOPs (Poli et al., 2008). These compounds, when tested either in tissue culture or examined in the context of the delicate respiratory system, are toxic even at a concentration of 1 µM. Surprisingly, at submicromolar concentrations (0.01–0.5 µM) tested in several cellular types, they can stimulate proliferation and useful biochemical activities. These findings lead to believe that toxicity of ozonated lipid products depends on the final concentrations and tissue-localization, for which they can act either as damaging or useful signals (Dianzani, 1998; Parola et al., 1999; Bosch-Morell et al., 1999; Larini et al., 2004; Aldini et al., 2006, 2008). Blood, compared with the lungs, is a much more ozone-resistant “tissue” and we have never observed any injury.

Kinetics of disappearance of LOPs from ozonated blood and reinfused was measured and its half-life in six patients with age-related macular degeneration (ARMD) was of 4.2 ± 1.7 min. On the other hand, same ozonated blood samples were incubated *in vitro*, and levels of LOPs showed a little decrease in the following 2 h, clarifying its possible toxicity in static cellular

cultures. In respect of cholesteryl ester hydroperoxide, Yamamoto (2000) has focused on the role of enzymatic degradation and hepatic uptake. Subsequently, toxicity of LOPs *in vivo* is irrelevant due to the following processes:

- (1) FORMATION OF ALBUMIN-4-HNE ADDUCTS. Assuming ozonation of 200 ml of blood with an ozone dose of 8 mg, the presence of about 5 g of albumin (Cys 34) is enough to form adducts with 4-HNE. In a total body pool of about 320 g of albumin, the ozonated aliquot is less than 1% (Aldini et al., 2006).
- (2) DILUTION (up to 150–200 folds) of these compounds in blood and body fluids occurring rapidly by which they lower their initial concentrations to pharmacological, non-toxic normal levels. Obviously the ozone dose must be within the therapeutic range.
- (3) NEUTRALIZATION of LOPs due to the antioxidant capacity of body fluids and cells.
- (4) DETOXIFICATION of LOPs due to interaction of billions of cells endowed with detoxifying enzymes, such as peroxidases, aldehydes and alcohol-dehydrogenases, aldose reductases and GSH-transferases (GSH-T) (Siems y Grune, 2003; Awasthi et al., 2005).
- (5) EXCRETION of LOPs in urine and bile after hepatic detoxification and renal excretion (Alary et al., 2003).
- (6) BIOACTIVITY without toxicity. As mentioned above, submicromolar concentrations of LOPs can act as physiological messengers able to reactivate an altered biologic system.

From a pharmacokinetic point of view, traces of LOPs can reach all the organs and, particularly, the bone marrow and the Central Nervous System (Fig. 4.9). LOPs are extremely important for they inform the cells on the minimum and estimated oxidative stress giving an adaptive response. With respect to erythrocytes, LOPs can influence the erythroblastic lineage thus producing cells with improved biochemical characteristics. These “supergifted erythrocytes”, as some of us name them, due to induction of glucose-6-phosphate dehydrogenase, a higher content of 2,3-DPG and of antioxidant enzymes over the following weeks are able to transport more oxygen to ischemic tissues. The consequence of repeated treatments, obviously depending on the volume of ozonated blood, ozone concentration and treatment frequency is, after several initial treatments, a cohort (approximately 0,8% of the pool) of “supergifted erythrocytes” entering daily into circulation and, which will inevitably replace the erythrocytes generated before the therapy. This means that, after a prolonged ozone therapy, erythrocyte population will include not only cells with different ages but also erythrocytes with different and functional biochemical capacities. During the course of ozone therapy a marked increase in G-6PD and other antioxidant enzymes in young erythrocytes were measured (Bocci, 2004). Cellular activation process is very dynamic and is not everlasting because blood cells have a well defined life expectancy and limited biochemical memory, therefore, the therapeutic advantage MUST BE MAINTAINED WITH PERIODIC TREATMENTS.

Toxicity in blood, biologic fluids and internal organs can be completely prevented when the ozone dose reduces, partly and transiently, the multiform and potent antioxidant capacity. Antioxidant system has evolved over the past two billion years as an essential defense against oxygen: it is made up of different components, mainly albumin, vitamins C and E, uric acid, bilirubin, cystein, ubiquinol, alpha-lipoic acid and intracellular antioxidants, such as GSH, thioredoxin and enzymes (superoxide dismutase, SOD, GSH-Px, GSH-Rd, GST-T, catalase, etc.) and proteins, such as transferrin and caeruloplasmin, able to chelate iron and copper that, otherwise, can favor the formation of hydroxyl radicals. The wealth and variety of extracellular and intracellular antioxidants, thoroughly described by Chow and Kaneko (1979), Halliwell (1994, 1999^a, b, 2001), Frei (1999), Holmgren (1989), Di Mascio et al. (1989), Jang et al. (1997), Packer et al. (1997), Bustamente et al. (1998) y Chae et al. (1999), are able to explain how specific amounts of ozone can stimulate various biologic systems, without deleterious effects. Not until this key concept is understood, the dogma of toxicity by ozone shall remain obstructing the possibility of extending the benefits from this excellent therapy.

Table 4.2 System of antioxidants

Non-enzymatic

Enzymatic

Hydrosoluble

Liposoluble

Chelating Proteins

Uric acid
Ascorbic acid
Glucose cystein
Cysteamine, taurine
Tryptophane
Hystidine
Methionine
GSH
Plasma proteins

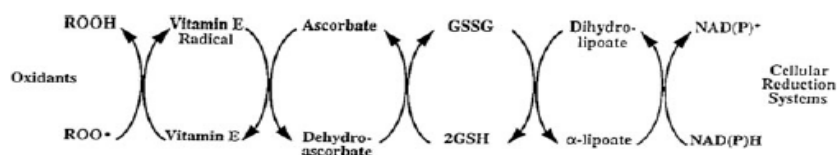
Vitamin E
Vitamin A
Carotenoids
Coenzyme Q
 α -lipoic acid
Bilirubin
Thioredoxina
Bioflavonoids
Melatonin
Lycopene

Transferrin
Ferritin
Ceruloplasmin
Lactoferrina
Haemopessin
Albumin

Superoxide Dismutase (SOD)
Catalase
Gluthatione peroxidase
Gluthatione redox system
Reducing equivalents via
NADPH and NADH

The interaction among antioxidants, enzymes and the metabolic system is very important and allows rapid regeneration as well as the maintenance of a normal antioxidant status.

The following scheme, drawn by Prof. L. Packer, illustrates the cooperation among different antioxidant systems aimed at neutralizing the lipoperoxide radical ROO• (illustrated at the extreme left side) turning it into a less reactive hydroperoxide, the ROOH. Reducing activity is continuously generated by cellular metabolism via continuous reduction of NAD(P)⁺ to NAD(P)H.



Suffice it to say that, during ozone administration to blood, the antioxidant reserves decrease not exceeding 35% in relation to the ozone doses between 20 and 80 $\mu\text{g/ml}$ of gas per ml of blood (4000 and 16,000 μg of total dose in 200 ml of blood). It is important to add that, in cases in which these parameters have been measured in samples of this blood maintained *in vitro*, partial reduction is corrected between 15 and 20 minutes thanks to recycling of dehydroascorbic acid, GSSG, alfa-tocopherol radical, etc. to their reduced compounds.

4.2 Natural oxidative stress and induced by oxidant therapies. Rational bases for an effective ozone therapy dosage.

The most important source of reactive oxygen in normal conditions in aerobic organisms is probably the loss of activated oxygen from mitochondria during normal function of oxidative breathing. Oxidative stress is inherent to superior aerobic organism's own life. This is easily understood, taking into account that our physiology has developed submerged in a gaseous environment with nothing less than 18% of oxygen, and that it participates fundamentally in the absolutely necessary processes for energy production as well as in many others of no less importance.

This has led to develop multiple mechanisms and substances involved in oxygen uptake. In the same way that from oxygen uncountable metabolites, processes and indispensable substances for life develop, likewise, the well-known Reactive Oxygen Species

"ROS" are produced, which have the capacity to damage multiple substances and vital structures. Therefore, in line with these processes, also different substances and processes have developed that, naturally, perform the function of controlling ROS levels and avoid proliferation of the damages they produce. Some of them have been commented on previous paragraphs. Those more effective enzymatic are represented in a scheme in Figures 4.10 and 4.11.

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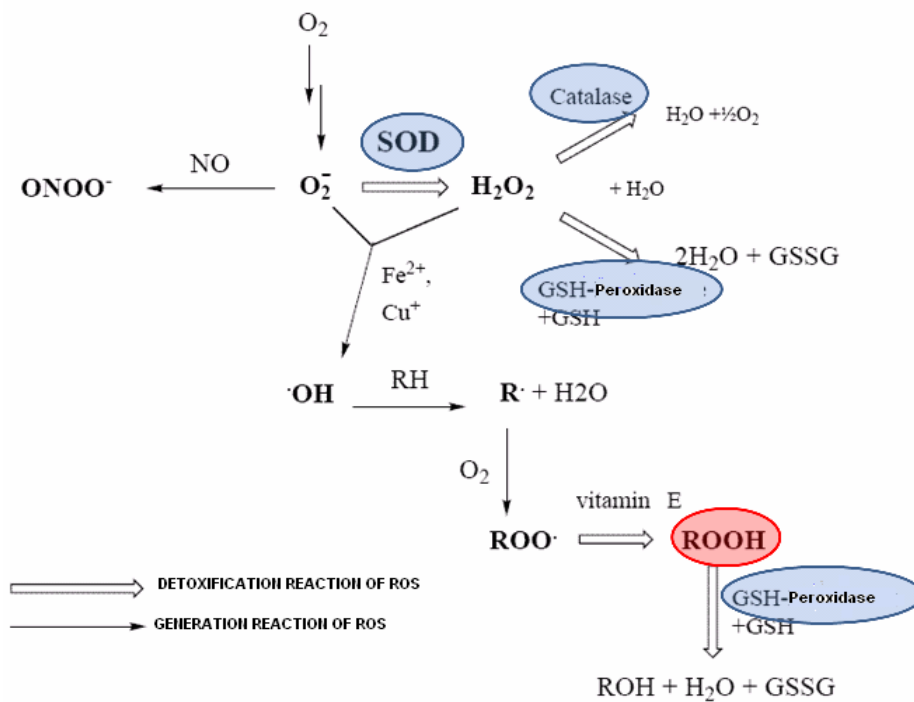


Fig. 4.9. Oxidative Stress is natural and physiologic and sharp rises of it are constantly produced during lifetime and multiple human activities, at the same time that ANTIOXIDANT mechanisms and substances are in charge of neutralizing and reestablishing its values to baseline level.

Regulatory events and their dysregulation depend on the magnitude and duration of the change in ROS and/or RNS concentration

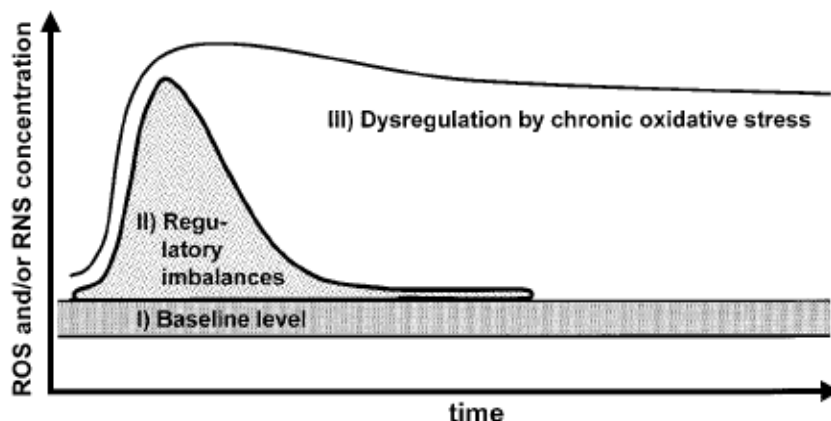


Fig.- 4.10. Only when, for some reason, generally pathologic, we cannot achieve to reestablish this equilibrium, then we are able to talk about CRONIC OXIDATIVE STRESS and consider it PATHOLOGIC AND POTENTIALLY DAMAGING.

As examples of everyday situations of transient oxidative stress, self-regulated by normal antioxidant mechanisms, we may say that, in principle, ALL THAT CAUSES US AN INCREASE IN OUR OXYGEN DEMAND WILL GENERATE AN OXIDATIVE STRESS. If our antioxidant defenses are under acceptable conditions, it will be transient and self-regulated. Examples: Food Diet, Hygiene, Physical Exercise, Physical Work, Stressful Situations (thermal, physical, psychological, etc.), Many Oxidant Medications (Adriamycin, etc.), some Oxygenating Therapeutic Procedures, etc.

The called "Postprandial Oxidative Stress" has been reported (Bloomer et al. 2010); it is shown in Fig. 4.11, where we observe increases in oxidative stress of about 100 % after intake of 150 g of glucose and up to 400% after 2 hours of lipid intake of 60 g.

Postprandial oxidative stress in response to dextrose and lipid meals of differing size

Richard J Bloomer*, Mohammad M Kabir, Kate E Marshall, Robert E Canale, Tyler M Farney
Lipids in Health and Disease 2010, 9:79

UNIVERSE: N=9 HEALTHY YOUNG MEN AGED 20-22 YEARS, WITH HEALTHY HABITS AND NOT TAKING MEDICATIONS

-AFTER 10 HOURS OF NIGHT FAST

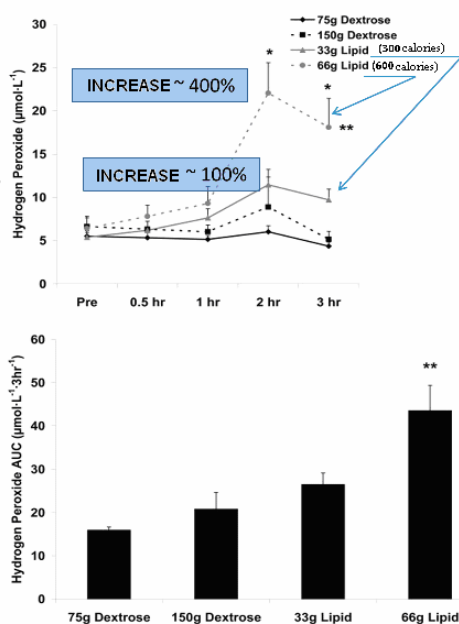


Fig. 4.11

Likewise, the level of lipid peroxides in blood and antioxidant enzyme activities behaving in accordance with the circadian periodicity in healthy subjects and in patients have been reported (Singh et al., 2004). This is shown in Fig. 4.12.

CIRCADIAN PERIODICITY OF PLASMA LIPID PEROXIDES AND ANTI-OXIDANT ENZYMES IN PULMONARY TUBERCULOSIS

Indian Journal of Clinical Biochemistry, 2004, 19 (1) 14-20
 Ranjana et al.
 Departments of Biochemistry, Medicine and TB & Chest Diseases, King George's Medical University, Lucknow.
 *Department of Biochemistry, G.S.V.M. Medical College, Kanpur, **Department of Community Medicine, Era's Lucknow Medical College, Lucknow

60 HEALTHY SUBJECTS
 50 PATIENTS WITH PULMONARY TUBERCULOSIS

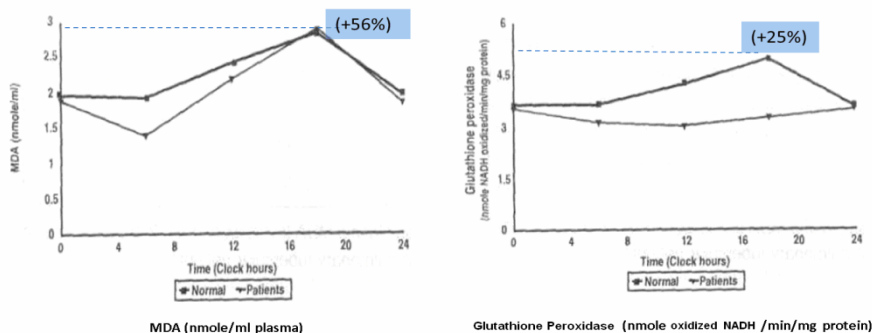


Fig. 4.12

Moreover, increases of oxidative stress could be exhibited (Marin et al. 2011) up to 118% in plasma and 152% in erythrocytes, 24 hours after strong warming up (Fig. 4.13).

Cytokines and Oxidative Stress Status Following a Handball Game in Elite Male Players

Oxidative Medicine and Cellular Longevity
 Volume 2011, Article ID 804873, 10 pages

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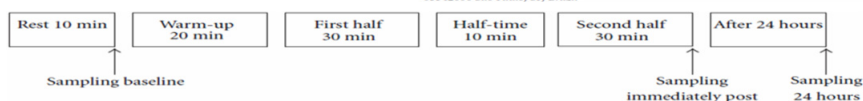


FIGURE 1: Experimental design.

14 male elite Brazilian handball athletes. Results before and after a single friendly handball game

TABLE 2: Plasma and erythrocyte TBARS levels, protein carbonyl, and thiol content of handball athletes. Results are presented as mean ± SEM. *Indicates significant differences in respect to baseline values (P < 0.05).

	Baseline	Postgame	24 h
TBARS			
Plasma (µmol MDA/mL)	0.11 ± 0.02	0.18 ± 0.01*	0.24 ± 0.02*
Erythrocytes (µmol MDA/mg of protein)	668.80 ± 50.87	595 ± 62.42	1687 ± 184.20*
Protein Carbonyls			
Plasma (protein carbonyls/mL)	16.16 ± 0.37	14.73 ± 0.58	14.64 ± 0.27
Erythrocytes (protein carbonyls/mg of protein)	42.77 ± 0.92	59.95 ± 2.94*	62.78 ± 2.30*
Thiols			
Plasma (mmol thiols/mL)	20.40 ± 2.09	8.23 ± 1.01*	16.67 ± 1.35
Erythrocytes (mmol thiols/mg of protein)	1.57 ± 0.29	1.22 ± 0.22	1.05 ± 0.21

PLASMATIC MDA INCREASE	µmol/ml	%	ERYTHROCYTE MDA INCREASE	µmol/ml	%
AFTER THE GAME	0,07	64	AFTER THE GAME	-73,80	-11,0
24H. AFTER THE GAME	0,13	118	24H. AFTER THE GAME	1018	152

Fig. 4.13

Regarding oxygenating therapies, Hyperbaric Oxygenation is an example. It is

considered "noble" therapy, accepted by sanitary authorities of all countries, about which second effects in very specific circumstances have been reported.

This therapy is able to generate a significant oxidative stress for an extended period of time, at least, during all the treatment and very likely until several more days. In Figure 4.14, an example is shown of a study conducted with 20 subjects, including volunteers and patients and 15 treatments. According to results, oxidative stress increase, measured by two different methods, becomes higher and sustained throughout the treatment. This is proven before last session where MDA in plasma reaches mean levels by 46% above the initial normal values, later on reaching up to a mean of 61% after last session.

Oxidative stress and antioxidant status in patients undergoing prolonged exposure to hyperbaric oxygen

Clinical Biochemistry 37 (2004) 312–317
 Serena Benedetti,^a Antonio Lamorgese,^b Michele Piersantelli,^a Silvia Pagliarini,^a Francesca Benvenuti,^a and Franco Canestrari,^a
^a Institute of Biological Chemistry "G.Fornaini", University of Urbino "Carlo Bo", 2-61029 Urbino (PU), Italy
^b Hyperbaric Medicine, Therapy and Research Center, Fano (PU), Italy

- 8 Volunteers

- 12 Patients (M = 8, F = 4, mean age: 57.5 ± 15.0 years)

PROTOCOL: 15 successive treatments of HBO, (1 session/day). Patients breathed 100% of O₂ wearing masks at a pressure of 2.5 AT. For a total of 2 periods of 30 min. with interval of 3 min. during which they breathed air.

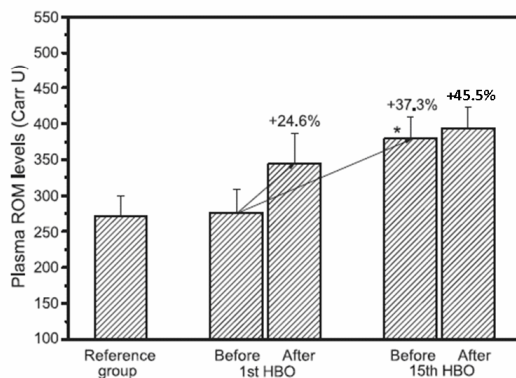


Fig. 1. Effect of HBO on plasmatic ROM levels (CARR U)
 *P < 0.05 vs. 1st HBO, t test for paired data

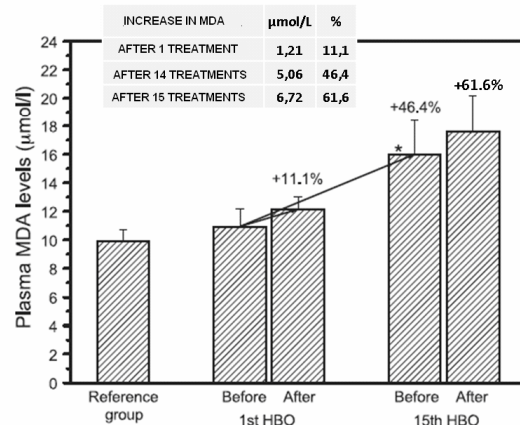


Fig. 2. Effect of HBO on plasma MDA
 *P < 0.05 vs. 1st HBO, t test for paired data

Fig. 4.14

Instead, in the case of Ozone therapy, oxidative stress caused by administration of a treatment cycle by major ozonized autohemoherapy (MO-AHT), compared with that produced by other causes is much less and self-regulated inherently while treated, thanks to its capacity of stimulating natural antioxidant enzyme systems.

This phenomenon is demonstrated in different clinical studies (Bocci, 2002), in which lipid peroxides in blood as well as some antioxidant enzymes have been measured during the treatment cycle.

Figure 4.15. shows how along 9 treatments carried out in a month period, initially, lipid peroxides slightly increase (without surpassing the considered reference levels), and from the 5th treatment on, SOD starts to activate sensitively and, consequently, the antioxidant defenses of patients are at a higher level of activity than before.

There are other clinical studies illustrating how, within the established threshold by basic studies undertaken and experience, one more intense and energetic treatment cycle by MO-AHT and with an increased ozone dose daily, can yield better results.

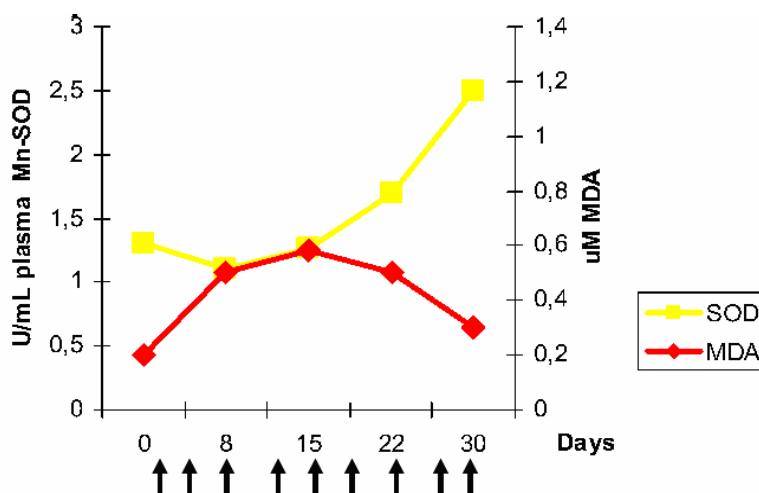


Fig. 4.15 Behavior of SOD and lipid peroxides (MDA) in age-related macular degeneration in patients treated with MO-AHT (Bocci, 2002). Arrows indicate the MO-AHT sessions.

One of this examples is comparing between outcomes from 2 independent studies (Hernandez F. et al. 1989 & 1995), but performed with a comparable protocol (15 session/day for 3 weeks), which differed from each other when ozone doses were applied daily, 5000 μg in one case, and 10,000 μg. Figure 4.16. shows behavior of LOPs and Activity of Glutathione Peroxidase (GPX) during the treatment cycle of both studies. It is observed that in the case where the highest ozone dosage was used, antioxidant effect was greater throughout the whole treatment.

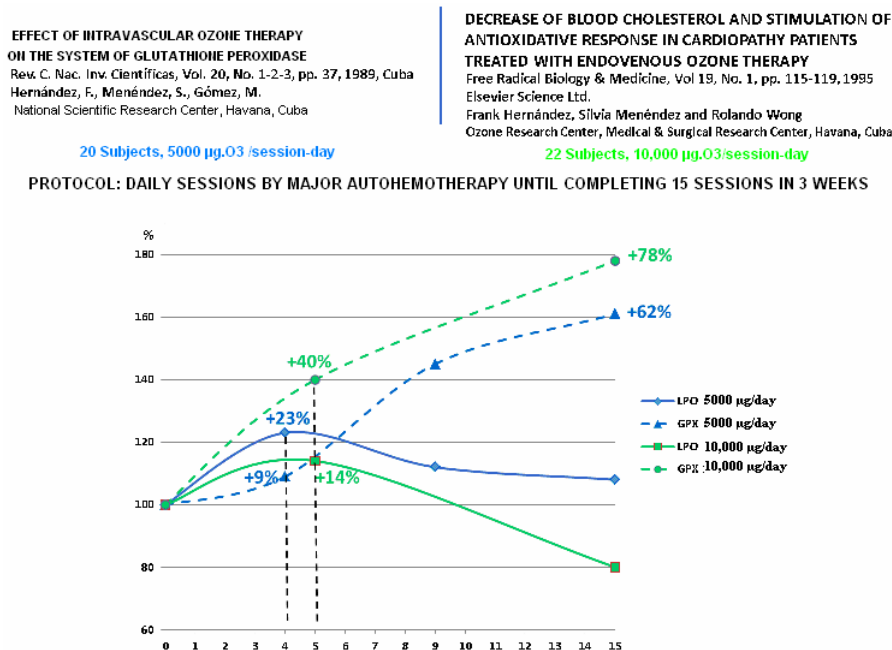


Figure 4.16. shows that between the 4th and 5th treatments, enzyme activations of 9% (lower dose) and 40% (higher dose) had been obtained and, consequently, increase of LOPs was of 23% (lower dose) and of only 14% with the higher dose. Activation of GPX with higher dose was produced up to a final higher activity level (78%) than in the case for the lower dose (62%). Final level for LOP was also much lower than the initial in the case of treatment performed with the highest ozone dose.

This can be understood due to the very specific capacity of ozone's metabolites produced, while interacting with blood, to activate natural enzyme defense systems very markedly.

Bearing in mind that maximum levels of oxidative stress obtained in these clinical studies with MO-AHT are greatly under the levels reported in plasma during many usual human activities (lipid intake: of +100 to +400%) (warming up +152%), circadian variations (+56%), as

well as the one produced by therapies considered as noble by the sanitary authorities (Hyperbaric Oxygenation: +61%), we must conclude that Systemic Ozone Therapy via MO-AHT, only generates a slight oxidative stress of very short duration and is very safe and nearly free of adverse side effects.

Conclusions.

When human blood is exposed to therapeutic doses of oxygen-ozone, both gases dissolve in plasma depending on their solubility, partial pressure and temperature. While oxygen establishes equilibrium between gaseous phase and plasma, ozone, ten-fold more soluble, cannot establish equilibrium because it REACTS IMMEDIATELY with biomolecules (PUFA, antioxidants) present in plasma and is totally exhausted. Reaction generates lipid oxidation products (LOPs) and hydrogen peroxide (among other possible ROS), that we could denominate as "metabolites of ozone". Sudden increase in hydrogen peroxide concentration generates a gradient causing it to rapidly transfer into blood cells where, in few minutes, activates several biochemical processes and simultaneously hydrogen peroxide is reduced to water by a very efficient intracellular antioxidant system (GSH, catalase, GSH-Px). This fundamental phase corresponds to a slight, controlled, acute and transient oxidative stress, necessary to biological activation, without toxic concomitant concentration, whenever the ozone dosage was compatible with the blood antioxidant capacity, which comparatively is very high.

While ROS are responsible for immediate biologic effects in blood, LOPs are key late effectors, when ozonated blood *ex vivo*, returns to circulation by reinfusion. When ozone is applied locally, both ROS and LOPs exert their effects in the tissue.

LOPs may reach every organ, particularly the bone marrow where, after inducing stimulation of cellular nucleus (NFkB y Nrf2), by means of intracellular variation of hydrogen peroxide and glutathione, induce adaptation to repeated acute oxidative stress. Due to prolonged therapy, activity of LOPs will end with overregulation of antioxidant enzymes, occurrence of oxidative stress proteins (heme-oxygenase I as typical marker) and probable release of stem cells representing crucial factors explaining some of the extraordinary effects of ozone therapy (Chapter 8). Recent paper of Bocci group (Pecorelli, A. Et al., 2013), confirmed by Re (Re L. Et al., 2014), demonstrated the involvement of the Nrf2 modulation following ozone treatment in humans. Nrf2 is a key protein responsible either of the cell detoxification (healing) or of the cell death (illness) (Zucker et al., 2014), thus demonstrating once more the importance to use the best ozone doses to reach the desired effect able to induce health benefit and not damage.

It must be emphasized that BLOOD EXPOSED TO OZONE UNDERGOES A SLIGHT AND TRANSIENT OXIDATIVE STRESS absolutely necessary to activate biologic functions without detrimental effects. The stress must be adequate (not subliminal) to active physiological mechanisms, but not excessive to overwhelm the intracellular antioxidant system and cause damage, though this threshold is very high. It is estimated that ozone doses that could be considered excessive for an average subject would be of the order of >30,000 µg of O₃ per session (Bocci, 2011). Concentrations over 80 µg/ml may exceed antioxidant capacities of some tissues (Greenberg 1993) and safety of greater concentrations has not been clearly demonstrated experimentally. On the other hand, a very low ozone dose (under the threshold of 2000 µg), is completely neutralized by the wealth of antioxidants and plasma unsaturated fatty acids and could only produce a placebo effect. In the same way, 1 mg of ozone per session in an MO-AHT treatment is useless to correct the oxidative stress compared to 5 mg (Borrelli, 2014). We have also checked (Hernandez, 2005) that for COPD patients, 4 mg improve the oxidative stress but don't improve the clinical parameters; on the contrary, 8 mg can improve both situations. Based on these experiences, is mandatory to establish an effective dosage on scientific research for each pathology.

THERAPEUTIC RESPONSE reached by repeated oxidative stress can be conceived as PRECONDITIONING EFFECT, able to reestablishing equilibrium and enhancing the redox system altered by pathologic causes.

Chapter 5

Ozone ways of administration.

Except for the inhalation route (prohibited by tracheo-bronchial-pulmonary toxicity), many parenteral and topical routes have been used to administer ozone without toxic effects and minimum discomfort (Table 5.1).

Table 5.1 Routes of ozone administration

<u>Parenteral</u>	<u>Topical or locoregional</u>
Intravenous (ozonated Autohemotherapy)	Nasal ^a
Intra-arterial (IA) ^b	Tubal ^a
Intramuscular (IM)	Auricular
Subcutaneous (SC)	Oral ^a
Intraperitoneal (IPE)	Vaginal
Intrapleural (IPL)	Urethral and intrabladder
Intra-articular (IAT)	Rectal
(A) Periarticular	Cutaneous
(B) Myofascial	Dental
Intradiscal (ID)	
Intraforaminal (IF)	
Intralesional (IL) ^c	

a To be performed during 30 seconds in apnea

b No longer used for limb ischemia. In hepatic metastasis can be embolized via hepatic artery

c Intratumor or via intra-abscess fistula.

The gas mixture, composed of no less than 95% oxygen and less than 5% ozone, produced by a medical ozone generator has a slight positive pressure and can be collected with a calibrated syringe (glass is ideal but impractical and has been substituted with polypropylene, silicone-coated syringes). If a continuous flow of gas is needed, an adequate connection can be incorporated to the exit valve of the ozone generator. RUBBER or LATEX TUBES CANNOT BE USED since they rapidly absorb ozone and disintegrate; hence, silicon, pvc, polyethylene, etc. tubes, inert to ozone are the ideal ones.

Although ozone is a potent disinfectant, ozone, as a dry gas, is withdrawn from a valve exposed to environment. Then, it must be filtered for medical applications to avoid possible contamination. Currently we use filters of sterile syringes. These filters are antibacterial, ozone-resistant and hydrophobic, made of tephlon and with 0.2 µm porosity.

Since 1984, due to a case of death produced by pulmonary embolism, DIRECT INTRAVENOUS AND INTRA-ARTERIAL ROUTES OF ADMINISTRATION, containing variable quantities of ozone HAVE BEEN ADVISED AGAINST by scientific associations. In the case of the DIRECT INTRAVENOUS, though the gas is slowly injected, it generates a current of gaseous bubbles, in which ozone (more soluble than oxygen) dissolves and reacts with blood, while oxygen, whose dissolution is very low in bloodstream, may reach the right ventricle and, then, enter the pulmonary circulation. We must remember that oxygen solubility at 37°C is only 0.23 ml per 100 ml of plasma liquid and, consequently, venous plasma cannot dissolve oxygen fast enough if the infusion rate is improper, bringing about formation of gas embolus. Also, the lack of preclinical studies about cytotoxicity on vascular endothelium and the proper infusion rate, together with the absence of formal studies, make this route absolutely not recommended at present.

In the case of DIRECT INTRA-ARTERIAL ROUTE, due to a small gas volume and gas fragmentation into the limb capillary bed, IA administration does not involve the risk of embolism; however, it has been proven that there are not any advantages compared to classic

major autohemotherapy or even rectal gas insufflation. Subsequently, it is no longer used because repeated arterial punctures can be avoided and intra-arterial injections induce precapillary contractions. Furthermore, practice of therapeutic embolism (with alcohol and cytotoxic compounds) for hepatic metastasis is currently in use and seems to be relatively useful. On that basis, it is possible then to postulate the slow intra-arterial administration (via hepatic artery) of 20-40 ml of gas with an ozone concentration of up to 80 µg/ml. The risk of producing embolism by oxygen is minimal since the gas will disperse to sinusoid and tumor capillaries, possibly, with direct toxicity by ozone in neoplastic cells without side effects as it can be the case with chemotherapeutic compounds. So far, this procedure has been tested with a patient with diffuse hepatic metastasis without side effects.

INTRAPERITONEAL and INTRAPLEURAL ROUTES are, as far as we know, used by Russian physicians, first using ozonated water to wash the purulent matter and then insufflating in the cavities 100-300 ml of ozone gas with concentrations ranging from 5 up to 50 µg/ml depending on the severity of the infection. Ozone rapidly dissolves to react with exudates, by which it can reduce infections. Moreover, stimulating vasodilatation and cellular proliferation, may bring about fast healing. This treatment does not damage the peritoneum, as we observed after trying insufflation up to 300 ml of gas in rabbits' peritoneal cavity with an ozone concentration of 20 µg/ml. There was no discomfort in animals or damages in the peritoneal lining observed in autopsy after 24 and 48 h. In our view, these routes should be assessed in peritoneal carcinomatosis and pleural mesothelioma: daily gas insufflations of 2-3 L were possible upgrading ozone concentrations from 5 to 10-15 µg/ml on the basis of the patient's reactivity. Ozone, during the first 5-10 min., can be directly cytotoxic in neoplastic cells, just like chemotherapeutic compounds, except for the advantages of preventing chemoresistance without toxic effects, bone marrow depression and mucositis, and at minimum cost. There is no practically embolism risk and advantageous transient local hyperoxia can not be disregarded. A permanent silicone cannula can be easily inserted in the cavities for everyday administration. Peritoneal dialysis has taught us all about the great potential of peritoneal cavity, where normally 1-2 L of solution is exchanged every 4-6 h to eliminate catabolites. Ozone kills directly neoplastic cells, activates resident macrophages and neutrophils, while absorption through lymphatic system of ozone messengers can induce cytokines such as TNF-alpha, IFN-gamma and IL-2, that can activate the immune system for completing cancer cells destruction. Likewise, preconditioning in rats that suffered an acute cardiac allograft with intraperitoneal ozone prolongs survival of graft (Stadlbauer et al., 2008).

Intra-articular, intradiscal and intraforaminal administrations are dealt with within the context of orthopedic diseases.

TOPICAL APPLICATIONS can be conducted, isolating lesions with bags or cups inert to ozone and insufflating the gas or with ozonated water and/or oil.

Nasal, tubal and oral conditions (gingival, mucosal and tonsillary) may be treated with adequate silicone or metal catheters. When the gas is used, a volume of approximately 20 ml (ozone concentrations from 5 up to 20 µg/ml) can be enough, but the patient, after taking a deep breath, must remain in apnea for 40-60 seconds and then breathe out to expel the ozone residues. Aphthas in oral cavity can be treated with intra-lesion mini injections of ozone (concentration: 5-10 µg/ml) followed by daily topical application with ozonated oil. So far, it is fashionable to use a silicone cup containing and exposing a herpetic lesion to ozone during 20-30 s (Section 9.16). Ozonated oil application on lesion is much more practical and economic.

Ozone treatment in chronic rectal and vaginal injuries (bacterial, viral, fungal and protozoal), resistant to conventional treatments, responds satisfactorily to ozone therapy. After inserting approximately 10-20 cm of silicon catheter (lubricated with silicone gel), we can start to wash the cavities with abundant ozonated water to remove purulent secretions. Then, we can insufflate 50-300 ml of gas (for vaginal or rectal cavities, respectively) for some minutes, being careful to lower the ozone concentration as the infection decreases. Vaginal and rectal pessaries and suppositories of ozonated oils can be applied before night sleep. Similar strategy can be used to treat urethral or bladder infections, keeping in mind to reduce ozone concentrations from 3 to 10-15 µg/ml, respectively.

Cutaneous applications include all types of infections (from pain to diabetic ulcers,

burns, and insect and jellyfish stings), accidents and traumatism. Gas can be used, but the injury must be airtight with materials resistant to ozone to prevent this gas leakage. For limbs, flexible bags are usually used and for other zones, cups with two connections to apply a vacuum and ozone. With vacuum capsules we can, according to Wekmeister (1995), enhance hyperemia, which is also convenient. In such cases, the physician needs an ozone generator equipped with a vacuum pump with a catalytic ozone destroyer. If a dynamic exposure was not feasible, the static system can be achieved by means of a polyethylene bag sealed with broad adhesive tape but not so tight so as to avoid venous stasis. Also a compress wet with ozonated water can be applied for approximately 20 min and next apply ozonated oil during the night.

There is no doubt about the ozone's powerful disinfectant activity (probably slightly less than iodine, in fact, very aggressive on tissues) with respect to Gram negative and positive bacteria, viruses, protozoa and fungi. Simple and inexpensive treatment with ozonated water and oil is well tolerated, do not have noxious effects and time for healing is much shorter than with any conventional treatment. The latter advantage is due to concomitant number of factors, such as disinfection, vasodilatation and oxygenation with normalization of tissue acidosis and reabsorption of edema. (Bertolotti and Izzo, 2006; Borrelli et al., 2008; Faus Vitoria, 2008). Theory sequence of wound healing has been schematically represented taking place in three phases (Martin, 1997).

Scheme presented in Fig. 5.1 shows the three phases: Phase I shows inflammation, generally lasting 2-3 days. Successive bacterial infection after trauma, diabetes, local ischemia and possible resistance to antibiotics, can become chronic unless we mediate with ozone therapy. Phase II corresponds to intermediate phase and generally lasts 2 weeks. It stimulates synthesis of extracellular matrix (fibronectin, collagen III/I, hyaluronic acid and chondroitin sulfate), and is accompanied by active proliferation of fibroblasts and keratinocytes. Use of ozonated oil not only prevents infection but also stimulates initial tissue reconstruction. Restitution ad integrum, i.e., Phase III, includes final healing and scar tissue remodeling. It can last longer for elderly and/or diabetic patients.

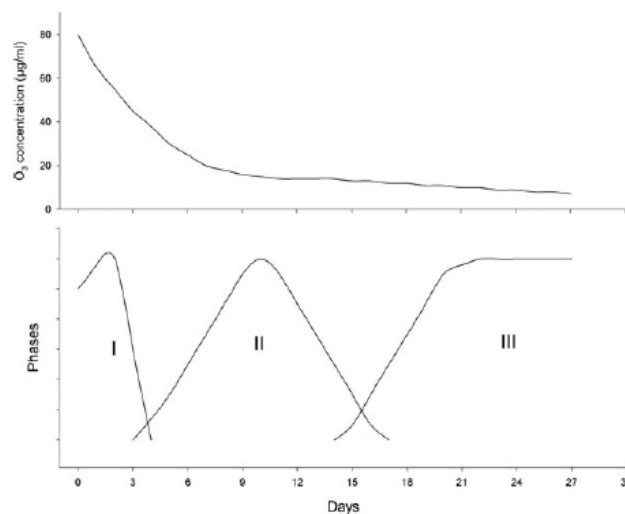


Fig. 5.1 The three phases of wound healing (Bocci, 2011). In the first (I) phase, inflammation prevails with presence of neutrophils, macrophages, mastocytes, platelets, bacteria and γ toxins. Ozone application inhibits infection and promotes the second (II) phase, which lasts approximately 2 weeks. During that phase, constant application of ozone with progressively lower doses not only prevents infection but also stimulates cell proliferation, synthesis of fibroblasts and keratinocytes. Restitution ad integrum, that is, complete reconstruction of wound, occurs during the last phase (III).

By experience, successful and relatively fast healing of necrotic ulcers in arteriopathic, diabetic and immunosuppressed patients may be achieved by parenteral treatment (autohemotherapy), and with adequate progressive reduction of ozonated water and oil concentrations. Strict control of glycemia and of these therapies combined seems to act synergistically. Topical use of antibiotics and growth factors is very expensive and often ineffective.

Conclusions.

The variety of routes for ozone administration has been mentioned. Despite inherent toxicity by respiratory route (which is totally excluded), if used with cautious doses, ozone is a versatile agent that can be remarkably useful in different diseases. Even in local infections or neoplasm in oral-nasal-pharyngeal locations, these can be treated whenever the patient can remain in apnea for about 40 s or has been intubated. Owing to false statements from folk healers, that direct IV administration of the gas can cure HIV infections, this route, as aforementioned, must be proscribed, since there are many other safer methods for ozone administration.

Regarding subcutaneous administration (SC), physicians treating lipodistrophies must inject small volumes (1-2 ml) of gas (ozone concentration: 2-3 µg/ml) in multiple sites completing a total of 80-100 ml per session. During continuous rest of approximately 30 min, injected zones can be massaged with ozonated oil. No negative side effect has ever occurred with this procedure even after distributed injection with 300-400 ml of this gas. Intraperitoneal and intrapleural administrations have been applied scarcely, but are of great interest in treating life-threatening peritonitis, empyema, peritoneal and pleural carcinomatosis and chronic viral hepatitis in patients undergoing peritoneal dialysis treatment.

Accidents and traumas, burns and all kinds of chronic cutaneous infections can be adequately treated with ozonated water and oil that compared to conventional creams are worthy of great attention. Topical uses in chronic ulcers present in diabetic and elderly patients lead to prompt healing.

Chapter 6

The three systemic therapeutic modalities.

Parenteral ozone administration may represent the key to sort out some medical problems when allopathic medicine has failed because it enables to administer rather "high" doses in order to achieve the expected beneficial effects.

6.1 Major Ozone Autohemotherapy (MO-AHT).

This term indicates the classical procedure by which a specific volume of blood is withdrawn from a peripheral vein, then exposed to oxygen-ozone for about one minute (according to the device used) and retransfused by the same route, (MO-AHT) or intramuscularly (mO-AHT) in the donor. "Major" and "minor" only differ according to the blood volume: 50-225 ml for the former and 5-10 ml for the latter. The original idea for exposing blood ex vivo to a gas mixture was proposed by Wehrli and Steinbart (1954), who published the method of blood irradiated with UV light in presence of pure oxygen. This procedure termed HOT (Hematogenous Oxidation Therapy) is no longer used due to uncertainty related to actual ozone concentration during UV irradiation of oxygen. Also the procedure was complicated and risky because the quartz ampoule had to be cleaned and sterilized after each treatment. In fact, some cases by cross infection with HCV, due to improper sterilization, were widely diffused and denigrated modern ozone therapy (Gabriel et al., 1996). This type of serious cross infections has taken place in the past due to doctors and nurses' negligence compromising ozone therapy's progress. In the 60's, reliable medical generators were already available and HANS WOLFF PROPOSED DIRECT EXPOSURE OF BLOOD TO OXYGEN-OZONE, with the advantage of being cognizant of its exact concentration. In 1974, reports referred that he used

this method in many patients without any difficulty.

For introducing ozone in blood withdrawn from a patient, diverse methods have been used along history, some of them posing certain risks and/or excessive handling. As example, there are the systems using soft bags like those for preserving blood in blood banks and having the great disadvantage of containing great amount of plasticizer, mainly around 43% of phthalates (Valeri et al., 1973; Lewis et al., 1977; Lawrence, 1978; Thomas et al., 1978; Callahan et al., 1982; Labow et al., 1986; Whysner et al., 1996). It has been demonstrated that ozone interaction with plastic from these bags provokes particles from them to come off and speed up partial dissolution of phthalates in blood, that later on will reinfuse into the patient and which consequences in both cases may be worrying. In fact, in Italy, where the use of these bags became generalized to a certain extent in the 90's, a wrongly named "allergy to ozone" was even reported (though difficult to happen due to simplicity and instability of the molecule), when, probably the causes of some slight fever reactions and discomfort were actually owed to the aforementioned factors. Also, using soft bags extends the blood withdrawal process considerably, since, in practice, butterflies used for this purpose must not be thicker than G21 or G19 (1.1 mm) as maximum.

Fortunately, by 2000, new plastic containers had been developed without plasticizers, inert to ozone and more solid and safer, counting on the European Commission certificate for their exclusive use in mayor autohemotherapy with ozone. With them, the "allergy reaction" has disappeared due to absence of phthalates and release of plastic microparticles.

At present 3 systems mainly coexist. They are closed, single use and disposable circuits:

1- A sterile and disposable system consisting of a plastic bag free of phthalates, which comes with a conventional transfusion system for collection–infusion of blood previously anticoagulated (anti-clotting) with sodium citrate and required needles to carry on with the procedure. There are several models, all of them homologated for their use in MO-AHT by different notified entities.

2- Rigid plastic container in sterile package especially designed to that, with 2 different tubings, one for blood, with its corresponding anti-clotting filter, and the other to apply the vacuum and ozone, alternatively, directly from the ozone therapy equipment. The vacuum can be applied in a controlled manner as well as measured with the modern machines thus extremely facilitating blood withdrawal and allowing completing the whole treatment in less than 15 minutes. Likewise, ozone which is subsequently introduced is measured in real time. The devise is also specifically homologated for MO-AHT.

3- Traditional glass bottle with vacuum pre-applied in factory where conventional transfusion equipment are connected for blood collection-infusion and syringes with needles for introducing ozone (Fig. 6.3). As anticoagulant in this system, i.v. sterile dissolution of sodium citrate 3.13% is generally used in mono-dose ampoules of 10 ml. with an effective anticoagulant effect only in vitro, disappearing once it infuses and dilutes in blood circulation. It is safe for almost every patient, even those undergoing treatment with anticoagulants (Warfarin, heparin, hirudin), antiaggregant pharmaceuticals (aspirin, dipyridamole, ticlopidin, clopidogrel) or thrombolytic agents (streptokinase, tissue plasminogen activator) or patients with hepatic conditions and low level of prothrombin. Heparin can be also used as anticoagulant, but its repeated use can worsen dis-coagulation and cause severe hemorrhages. Notwithstanding, considering the abovementioned restrictions, only by means of a thorough analysis of the patient, the physician will be able to choose the suitable anticoagulant.

Diverse modifications to ozone administration in blood have been attempted, which should be mentioned briefly: first modification (patented in USA) uses hollow capillary fibers, (like filters for hemodialysis) but is expensive and unnecessary complex for which it has failed. The second system breaks up the gas in small bubbles through the blood, putting forward that this increases absorption velocity of ozone in blood. However, infusion velocity of ozone in bottle indicated by the manufacturer must be strictly followed because excessive bubbling

produces certain degree of hemolysis and lot of foam.

Blood volume withdrawn for ozonation must be flexible and keep a relationship with patient's body mass as well as the kind and phase of his/her disease. The international consensus (Klein, Anstee, 2014) on the maximum amount of blood for donation with minimum risk of faint or other hypovolemic complications is a 13% of the calculated total volemia, expressed in the following formula:

$$\text{ml to withdraw} = \frac{\text{donor weight (Kg)} \times 450}{50}$$

Depending on the hemoglobin level and the cardiovascular status of our patients, this amount should be adjusted. Trying to get a safe margin for avoiding hypovolemic side effects, no more than 225 ml of blood (for an individual of 75 kg - it is a 30% of the theoretical safe amount for donation) should be withdrawn to a sterile container, inert to ozone, with, at least, double capacity of blood draw volume, or homologated kit for MO-AHT. In Europe, many consider that a maximum of 100 ml of blood is optimal, although recently prevailing view of considering the body mass of the individual feeling 100-150 ml the minimum and maximum range for a person of 75 kg. This means that for a patient weighing 100 kg, the recommended amount of blood will be taken between 130 and 200 ml while in the case of a subject of 50 kg between 70 and 100 ml, depending on the disease to be treated and the patient's general condition. It is evident that ozone administered with any of these blood volumes generate crucial messengers such as ROS, LOPs, intermediate metabolites and autacoids which dilute, degrade, and excrete but which after interacting with cells, express key pharmacologic effects as long as we surpass the 4 mg of ozone, as mentioned in chapter 4.

Standard accuracy consists in undertaking 2 or 3 weekly treatments during 10-15 sessions. This program is a practical, very effective as proven in the great majority of patients. However, it can be modified to meet individual needs.

Adequate reinfusion of 100 - 225 ml of the previously withdrawn blood plus the 10% in ml of citrate solution can usually last between 5 and 15 minutes without any problem or complication for the patient. Nevertheless, we must check hemostasis carefully and avoid hematic extravasation that could compromise the course of therapy.

An important issue to highlight is that over the past 15 years, during dozens of thousand treatments carried out and reported in studies presented in multiple congresses of the sector and published internationally in Spain as well as in many European countries, such as Germany, Italy, Austria, Switzerland, Portugal, etc., no significant side effects have ever been reported. Sort of transitory slight dizziness similar to a sudden hyperventilation could rarely be produced. This could be related with transitory increase in the amount of oxygen transported to tissues, produced by MO-AHT.

6.2 Minor Ozone Autohemotherapy (mO-AHT).

In the 50's intramuscular injections were used, from recently withdrawn autologous blood, sterile milk as well as unspecific immunomodulators. This is an old practice and still used without ozone (Olwin et al., 1997). Wolff was able to have the idea of ozonating blood with the expectation of activating its components.

The technical procedure is empirical and simple: first, peripheral blood is withdrawn (5 ml) in a syringe of 10 ml and immediately after, by means of two-way stopcock, equal filtered oxygen-ozone volume is added with an ozone concentration between 40 and 80 µg/ml depending on the scope of treatment and the disease. One can also first collect 5 ml of gas from the ozone generator and, then, withdraw 5 ml of blood from the patient with same syringe. In both cases, the blood, mixed with the gas, absorbs and reacts with ozone immediately. After disinfecting skin on buttock and checking that no blood vessel has been penetrated, the

ozonated blood is injected in glutei, slowly without pain. We can carry out multiple injections and/or repeat them 2-3 times per week.

Logic of this unspecific kind of protein therapy enhanced by ozone is hypothetical and adequate scientific research would be needed. At the moment, we can speculate that blood, without anticoagulants, can infiltrate into muscle tissue or subcutaneous cell tissue and be able to coagulate due to platelet and prothrombin activation. If we take too long to inject, the blood will probably coagulate in the syringe.

Different processes such as fibrinolysis, reabsorption via lymphatic vessels and an inflammatory reaction are likely to occur occasionally, due to slight swelling on the site of injection, reported by several patients over the following days. Chemotactic compounds released on the site of injection may stimulate local infiltration of monocytes and neutrophils absorbing hemolysed erythrocytes and denatured proteins. Activated monocytes and lymphocytes can release interferons and interleukins, regulating physiologic response to cytokine (Bocci, 1981c, 1988a). Therefore, it is most interesting to assess immunologic parameters and determine if there is simultaneous induction of heme-oxygenase-1(HO-1) and other heat shock proteins (Tamura et al., 1997), which can enhance immunologic reactivity and explain the beneficial effects.

mO-AHT is easy to perform; it is atoxic, economic, and if we could conduct a controlled clinical trial, it would become a useful tool for some condition. So far, we only count on anecdotal data from patients with herpes I and II, acute herpes zoster and neuralgia post-herpetic neuralgia (Konrad, 2001).

The problem of new vaccines is becoming urgent and the use of ozone has been proposed as agent able to eliminate infectivity, while improving immunogenicity of a pathogen (Bocci et al., 2009b).

No side effects have been reported with mO-AHT, despite a great deal of experience.

6.3 Rectal insufflation with Oxygen-Ozone (RI).

In 1936 Payr and Aubourg were first in using insufflation of this gas-mixture through colon-rectum, and today, this approach is being undertaken in Cuba, since it is very easy to do, with just a few means, very cheap and barely without risks. In several USA states, many patients with AIDS used to make their own insufflations by using a portable inaccurate ozone generator. In California, Carpendale et al. (1993) were able to conduct a study in patients with AIDS with abundant diarrheas due to opportunistic infections of *Cryptosporidium*; and as expected, some patients reported temporary improvement. Carpendale was a clinical scientist who resorted to ozone as last alternative to patients in desperation. Diarrhea diminished but was not cured, as ethically confirmed the author.

The main field of application is represented by the anal and rectal abscesses with fistulae, proctitis, bacterial and ulcerative colitis, Crohn's disease and chronic viral hepatitis B and C. Even ischemic diseases and dementia disorders have been treated by RI, since it was postulated to have a systemic effect. In fact, a systemic effect seems to be supported by studies in rats (León et al., 1998; Barber et al., 1999; Peralta et al., 1999, 2000; Borrego et al., 2004; Gonzalez et al., 2004), where it was demonstrated that with RI for 2 weeks, cellular redox homeostasis is achieved.

Though every year hundreds of thousands of treatments are carried out, it is not clear the effect produced by gases administered by the glut route and if they could influence some physiologic, biochemical and immunologic parameters. Though the main approach to systemic ozone application is the MO-AHT, and official medicine underestimates this empiric treatment, as it is often the case, we have considered that it is important to analyze, regarding RI, the following questions:

- (1) How are oxygen and ozone absorbed by the gut mucosa?
- (2) Does RI have only local effects or also systemic ones?
- (3) Taking into account the toxic effects of ozone, in the respiratory tract, it is uncertain if ozone has a negative effect on the gut mucosa.

Knoch et al. (1987) examined modifications of PvO₂ after rectal insufflation in rabbits. They found an increase in the content of oxygen of 230, 121 and 127% in the mesocolonic vein, portal vein and liver parenchyma, respectively, between 8-20 min after rectal insufflation of 150 ml of the oxygen-ozone mixture. Values returned to baseline after 50 min. This result is not new since we know that some gases such as carbon dioxide, methane, hydrogen, oxygen and hydrogen sulphide either ingested or produced by the bacterial flora are partially absorbed, excreted or even exhaled with expired air. Obviously, we are interested in the fate of ozone introduced by RI. In Chapter 4, it has been clarified that ozone firstly dissolves in water, but unlike oxygen that diffuses freely to other compartments, it immediately reacts with any biomolecule, particularly PUFA, producing ROS and LOPs. Thus, we can determine the fate of ozone by measuring LOPs in the intestinal-portal system and in peripheral circulation. While the respiratory mucosa is overlaid by a thin and resistant film of fluids, the gut mucosa is abundantly covered by glycocalyx and a thick coating of water containing mucoproteins and other secretion products with potent antioxidant capacity (Halliwell et al., 2000). Besides this mucus-gel layer, a variable fecal content is present and may absorb the entire oxidant activity of ozone. It is clear that this unpredictable parameter is the weak point of RI, since, then, we cannot be sure of the actual available dosage of ozone. Notwithstanding, we thought it was worthwhile to research in rabbits if ozone, through LOPs, has local and/or systemic activity. Results have been elucidating as well as widely reported by Bocci et al. (2000) and Bocci (2002).

The following data are interesting in these studies:

- (1) After rectal insufflation, possible increase in the content of oxygen in the portal vein (20-35 min later) and in the jugular vein (35-40 min later) was measured. There were not significant changes of PvCO₂ and of pH.
- (2) Concomitantly, there was an increase in LOPs' values up to 60 min after gas insufflation, which is when they started to decline. Values were markedly higher in portal blood than in jugular blood, partly because of dilution in general circulation. On the contrary, values obtained from measuring oxidation of thiol groups have shown an opposite trend, reaching the minimum after 90 min. Both parameters returned to baseline level 24 h later.

Therefore, RI seems to exert a rapid local and systemic effect due to absorption of ROS and LOPs generated by ozone interaction with biomolecules present in content of gut lumen. The amount of ROS and LOPs absorbed is, however, unpredictable, due to the variable content of lumen, mainly fecal material.

One could think that ozone rapidly dissolves in luminal water, but compared to oxygen, it is not absorbed since part of it reacts with mucoprotein layer of mucosa or with fecal material and the remaining part is reduced by antioxidants. LOPs, such as oxygen, pass through muscularis mucosa (MM) and into circulation via the lymphatic system and venous capillaries. Conclusion is relevant and may support the thesis that beneficial effect of RI in chronic ischemia of limbs can be similar or equivalent to MO-AHT. If this outcome can be confirmed in a controlled and randomized clinical trial, it will be useful for patients with difficult venous accesses. Also, it would explain why prolonged RI (up to 13 weeks) in elderly subjects cause a modest increase in both, ATP and 2,3-DPG in erythrocytes (Viebahn-Hänsler, 1999a, b). These results are even more surprising because, compared with accurate volumes and concentrations of ozone, controlled in MO-AHT, we know well how inaccurate RI application of ozone may be and, particularly, the retained gas volume as well as that efficiently acting in the lumen.

This leads to discussion of some technical aspects in terms of gas volume, ozone concentration and administration schedule. RI should be done after defecation or after an enema, when the rectal ampoule is empty. Patient must be lying on one side and try to relax; the probe (30-40 cm long), of polyethylene and inert to ozone (rubber or latex must never be

used), lubricated with silicone, must be introduced slowly for 10-15 cm. Insertion is easy and must not stimulate peristalsis. At this point, the gas has to be introduced slowly and in steps of 50-100 ml very 1-2 min. If done very fast, the gas can cause discomfort and be rapidly expelled. The gas can be introduced via: (a) a two-way silicone pump connected to the gas collected in a polyethylene bag, or (b) a silicone-coated syringe of 50 or 100 ml, closing the catheter with Klemmer clamp after each insufflation. We can achieve good performance if we start from 100-150 ml and slowly scale to about 400-500 ml as the patient can tolerate. This volume can be easily retained for at least 20-30 min. Koch et al. (1987) insufflated up to 800 ml in 1 min. Carpendale et al. Insufflated from 700 to 1300 ml of gas (up to 30 mg of everyday ozone) in patients with AIDS, hoping that the gas could diffuse throughout the whole colon. The patient must rest for, at least, 15 min after RI to avoid expelling the gas and allow ozone to react with the lumen content.

Ozone concentration is important for inducing local and generalized effects but there is a general consensus that it should not exceed 50 µg/ml., except in pathologies treated in active bleeding phase where a higher concentration is recommended (up to 70 µg/ml.), which tends to enhance the hemostatic effect, as well as low volume, so as not to distend the mucosae.

For diabetic patients, Cuba's Health Care System has chosen to administer 200 ml of gas at an ozone concentration of 50 µg/ml (doses of 10 mg), in cycles of 20 treatments, applied on a daily basis.

After millions of applications, we may say that RI, if adequately conducted, does not appear to induce local side effects. It seems reasonable to think that with a sensible ozone dosage, the mucosa layer, the antioxidant system and adaptive response of erythrocytes are responsible for the absence of toxicity.

In Chapter 9, we will briefly examine pathologies where RI is better applied, though here it may be useful to hypothesize about possible local effects of ozone. These would be the following:

- (a) Biochemical effects. Studies already cited (León et al., 1998; Barber et al., 1999; Peralta et al., 1999, 2000; Borrego et al., 2004; Gonzalez et al., 2004), have shown that RI in rats upgraded the enzymatic antioxidant response in liver and kidney.
- (b) Bactericidal effects. The human colon-rectum contains up to 600 g of about 400 different species of anaerobic bacteria - ozone may partly change the environment for a short while. Except in particular conditions, like clindamycin-associated enterocolitis (Schulz, 1986), bactericidal activity per se is probably unimportant but may cause the release of lipopolysaccharides (LPSs) and muramyl peptides. These compounds are among the most potent cytokine inducers and in great quantities are responsible for the toxic shock syndrome and, probably, death. Despite this fact, in physiological conditions, daily absorption of traces of LPSs bound to specific proteins and to lipoproteins is considered essential to maintain the basic cytokine response and an alert immunologic system (Bocci, 1981b, 1988c, 1992c). Specifically, in the last article, it was postulated that, somehow, the underestimated gut flora has a crucial immunostimulatory role. This idea remains valid today and it is possible that RI favors a slight increase of LPS absorption with the consequence of activation of intrahepatic lymphocytes, Ito's and Kupffer's cells (O'Farrelly and Crispe, 1999), which may change the course of chronic hepatitis.
- (c) Modification of the bacterial flora equilibrium. Owing to the multiplicity of bacterial species, this remains a complex area. The normal flora contains *Lactobacillus* (Lb) *acidophilus*, Lb. *Bifidus*, Lb. *Fermentum*, Lb. *Casei*, *Streptococcus faecalis*, *S. Thermophilus*, *S. Bulgaricus*, *Escherichia coli*, *Proteus* and a variety of enterocci. The bacteria and their products interact with each other and with the enterocytes, calciform cells and enteroendocrine cells (producing innumerable hormones) and the gut-associated lymphoid tissue, (GALT) (Hooper y Gordon, 2001). On the other hand it is well-known that contaminated food, water and antibiotics can reverse this dynamic symbiosis allowing settlement of bacteria and fungi such as *Candida albicans*, *C. Tropicalis*, *Torulopsis glabrata*, etc. The successive and usually far

reaching dysbiosis has deleterious consequences, ranging from transient to chronic enterocolitis and to autoimmune reactions that, consequently, we must try to correct in order to repair normal homeostasis. Whether RI with a daily application of oxygen-ozone can reequilibrate the bacterial flora and lead to normal immunoreactivity remains to be demonstrated and explained, although empirical results suggest a beneficial effect.

- (d) Effects on GALT. The gastrointestinal compartment represents almost 40% of the whole immune system. Besides the famous plaques described by Johann Konrad Peyer (1653–1712), over a total intestinal surface of some 300 m², there are about 10¹¹ immunocytes per m² or about one per 6–7 enterocytes.

Intra-epithelial immunocytes are mainly T lymphocytes, either α - β of thymic origin or γ - δ of local origin. The latter induce a Th-2 type response that is anti-inflammatory and immunosuppressive, quite important to prevent excessive stimulation due to alimentary, bacterial, viral and toxic antigens. Perdue (1999) has emphasized that a continuous cross-talk between immunocytes and enterocytes may maintain a healthy homeostasis and prevent breakdown of the mucosa and inflammation. In spite of interesting hypotheses (Fiocchi, 1998, 1999; van Parijs and Abbas, 1998; Okabe, 2001; Shanahan, 2002; Ardizzone and Bianchi Porro, 2002), the etiology and pathogenesis of both ulcerative colitis and Crohn's disease remain uncertain and it is difficult to identify those responsible for gradually causing the disease.

Over the past 20 years, official medicine has made a great deal of effort to sort out this complex issue. Even today Crohn's disease still remains to be a serious condition. D'Ambrosio (2002^a, b), in an open study, has demonstrated that oxygen-ozone RI can enable notable improvement of these conditions. If his results are confirmed, no patient should miss this opportunity and undergo ozone therapy on a rationale basis.

Finally, by recalling that the gut is the biggest endocrine organ in the body and like our second brain contains billions of secretory neurocytes (Ahlman y Nilsson, 2001), it may be possible to speculate that we could use both RI and MO-AHT to influence or bring to normal condition the neurosecretion of relevant neuromodulators, which can be responsible for irritable bowel. Spastic colon is a difficult chronic disease with a high social cost that affects quality of life of many people under stress in everyday activity.

Chapter 7

Potential side effects and contraindications of Ozone Therapy.

One reason for ozone being so unpopular within medical field is because ozone toxicity is considered the same as that of ROS. In fact, there are considerable differences since ozone therapy is occasional and can be controlled, while endogenous formation of ROS does not practically suffer any alterations during lifetime (Farber et al., 1990; ames et al., 1993).

Topography of ROS formation is likewise different: mitochondria, which convert 95% of the inhaled oxygen to harmless water, are the main source of ROS since at least 3% of oxygen is converted to superoxide O₂⁻, (Richter et al., 1988, 1995; Halliwell, 1994). Dismutation of superoxide by SODs (Fridovich, 1995; Carlsson et al., 1995) is the source of H₂O₂ which, in the presence of Fe²⁺, may generate the fearsome, non-specific hydroxyl radical, OH•. Halliwell (1994) estimated that a 70 kg human produces no less than 0.147 mol or 5 g/day of superoxide, whereas one MO-AHT using a maximum of 18 mg of ozone, could produce an equivalent amount to less than 0.4% of the minimum daily production of superoxide.

Other small amounts of hydrogen peroxide are directly generated by oxidoreductases known as NADPH oxidases (NOXs). There is now consensus that the normal production of hydrogen peroxide is essential for the cell life and the revised concept is that "reactive species are not merely instruments of cellular suffering but of normal cellular physiology" (Forman et al.,

2008).

Endogenous ROS formation in mitochondria explains damage to mitochondrial DNA (Wiseman and Halliwell, 1996; Kowaltowski et al., 2009), which is oxidized approximately tenfold compared to nuclear DNA oxidation (Richter et al., 1988) and remains persistently damaged (Yakes and Van_Houten, 1997). On the other hand, ozone acts from outside on the plasma which has a great antioxidant reserve. Notwithstanding, the ozone dose added must reach a threshold aimed at generating sufficient H_2O_2 , of which only 10% passes from the plasma to the erythrocyte cytoplasm where several biological effects are activated. For ozone to act, we must induce a small, calculated, transient and acute oxidative stress which is rapidly corrected by the antioxidant system. Therefore, there is no doubt about the formation of peroxyl radicals and hydroxyaldehydes, while traces of $OH\cdot$ and $HOCl$, if present, are rapidly neutralized by a variety of antioxidants in plasma. In fact, it is important to highlight that all vital cellular components, such as enzymes, proteins, RNA and DNA (Van der Zee et al., 1987; Stadtman and Oliver, 1991; Ames et al., 1993), will be kept safe thanks to extracellular ozone decomposition.

Knowing the significance of oxidative DNA lesions in ageing and cancer, it would not be surprising to ask ourselves: ¿is ozone mutagenic? ¿Does ozone therapy speed up the ageing process?

This issue has been thoroughly covered in several articles in these matters (Bocci, 1996b, 2002, 2004). Generally, results have been controversial, because some authors (Goldstein and Balchum, 1967; Freeman et al., 1979), while working with erythrocytes washed with saline solution or tissue cultures without antioxidants, have observed damages or mutagenic changes in cells expose to ozone over a specific time period. Once cells are washed in protein-free saline solution, thus eliminating antioxidants, both oxygen and ozone become cytotoxic, just as Halliwell (2003) and Bocci (Larini et al., 2003; 2004) have remarked. Recently, Galleano and Puntarulo (1995), Leist et al. (1996), Matos et al. (2000) and Dumaswala et al. (2000) have also demonstrated that cellular damage and genotoxicity induced by hydrogen peroxide or iron saturation or prolonged storage are prevented if tissue culture or plasma have the adequate physiologic amounts of antioxidants.

Victorin (1992), who has reviewed this topic, stated that "no cytogenetic effects have been reported for bone marrow cells or spermatocytes and the few experimental and epidemiological studies with human subjects do not allow a conclusion on the cytogenetic effects of ozone in human lymphocytes". The most recent study by Diaz et al. (1995) is interesting, since it was performed in lymphocytes from eight patients with Retinitis pigmentosa, before and after 15 treatments with MO-AHT. Results did not show significant differences in sister chromatid exchanges (SCE), micronuclei frequencies and proliferation index values between control and ozone treated lymphocytes. On the other hand, Diaz-Llera et al. (2002) demonstrated that 1 h exposure of SALINE DILUTED BLOOD to 5 mM of ozone induces genotoxic effects in human leukocytes. However, during MO-AHT, THE WHOLE BLOOD (200 ml.) is exposed for just a few minutes to an ozone dose between 0.08 and 0.33 mM, and due to this much lower concentration is why we can explain that ozone is non-mutagenic in practice. A detailed study by Shinriki et al. (1998) has proven neither cellular damage nor hemolysis of human blood exposed to this therapeutic technique, at ozone concentrations up to 100 $\mu\text{g/ml}$ per blood ml (total 0.42 mM); Greenberg (1993) reported leukocytes damage at 90 $\mu\text{g/ml}$ and higher concentrations. This is the reason why we advice not to use concentrations over 80 $\mu\text{g/ml}$ in MO-AHT.

Concerning tumor induction by inhalation route, pulmonary adenomas were induced in sensitive A/J strain, but not in Swiss-Webster male mice, after 4.5 months of inhalation exposure to 0.8 ppm of ozone (Last et al., 1987). Witschi et al. (1999) conclude that studies in animals do not underlie the idea that ozone is a pulmonary carcinogenic agent.

In short, it seems that absence of natural antioxidants is critical and is the one that enables mutagenic changes in cells exposed to ozone *in vitro* over a time period. After removing plasma, washing and resuspension in physiological medium with or without a small amount of antioxidants, the erythrocytes and other cells (Larini y Bocci, 2004) become more sensitive at even very low ozone concentrations as demonstrated by intense haemolysis or

apoptosis. Instead of stigmatizing ozone therapy as toxic, many of the articles published (Goldstein y Balchum, 1967; Gooch et al., 1976; Freeman et al., 1979; Sato et al., 1999; Fukunaga et al., 1999), and drafted under artificial conditions, that had nothing to do with ozone therapy, should have emphasized the importance of the great number of physiologic antioxidants preventing possible damages.

Another mistake made by many is basing their statements about ozone therapy on experiments undertaken by cell biologists (often oriented to environmental ozone toxicity and/or the big industry of water potabilization with ozone) consisting in maintaining cell cultures constantly exposed to ozone (Merz et al., 1975; Tarkington et al., 1994) at very low levels but for several hours or days. Conclusion that ozone is toxic by therapeutic methods, even at minimum levels, is wrong, since the level of antioxidants in tissue cultures is much lower than in plasma and tissues, and most important, because of the cumulative ozone dosage over prolonged time. Though we have mentioned it up to this point, it is worth remembering that ozone solubility is very high: according to Henry's law, every second that ozone solubilizes in water, it reacts and disappears so that more ozone solubilizes and reacts: a process that will continue occurring in some of those experiments for days. Even small, this ongoing ozone supply to culture leads to an increase of H_2O_2 , $OH\cdot$, 4-HNE, etc. which is maintained and not extinguished due to the lack and exhaustion of a few antioxidants and, subsequently, it becomes toxic. Therefore, with long-term exposure, even the lowest ozone concentrations will rightly become toxic.

However, in usual application techniques, blood exposure to oxygen-ozone is performed with ozone concentrations within the therapeutic window and is completed after a few minutes. In this assertion we do not include the use of ozonated saline solution (a technique applied in some countries of the former Soviet Union), which is an error, due to immediate formation of sodium hypochlorite and hypochlorous acid HOCl, from chloride ion. A typical example is represented by slow IV infusion of ozonated saline solution: Foksinski et al. (1999) administered in patients with peripheral occlusive arterial disease (POAD) 500 ml of ozonated saline solution for 1 h without taking into account the great amount of HOCl formed; an increase by 450% of 8-hydroxy-2-deoxyguanosine (8-OHdG) was observed in lymphocyte isolated DNA of some of these patients. 8-OHdG is a marker of DNA oxidation. Thus, Foksinski's results should discard (as clarified in Chapter 6) the use of ozonated saline solutions. Similarly, therapeutic results from treatment were minimum compared to the usual ones from MO-AHT common technique. This is not surprising, since ozone dosages that can be administered with saline solution are extremely low. Lets recall that normal antioxidant capacity of plasma present in individual variability is approximately 1.3 to 1.8 mM (Miller et al., 1993), added to the high content of unsaturated fatty acids in diverse forms, whether in blood or in almost all the tissues, protecting blood cells more than enough as well as other tissue cells while ozonation within the therapeutic range.

A reassuring fact is that after million sessions of MO-AHT undertaken in Germany, Austria, Switzerland, Cuba, Italy and Spain, no acute or chronic second effect have ever been reported and not even yet any effect on cancer incidence.

In conclusion, though ozone is potentially toxic and mutagenic, so far, our research data and clinical evidence have proven no risk at all. A doctoral thesis from Jacobs (Germany, 1982) examined in detail all possible negative effects from ozone therapy in a sample of million treatments. Despite of the famous ozone "toxicity", seems that the incidence of only 0.0007% is one of the lowest in medicine. Four deaths by IV direct injection of the gas (currently proscribed) were included in the data and, therefore, since 1982 all Ozone Therapy Associations have advise against or forbidden this method. Ever since, only 3 cases took place in Italy due to this bad practice in the early 90's, due to IV direct injection performed in aesthetic cabins, applied by non-qualified professional personnel that lead to a temporary prohibition in this country until the real cause for death was cleared up.

In Cuba, MO-AHT began to be applied in 1986 in the Public Hospital, Instituto de Angiología y Cirugía Vasculat (Institute of Angiology and Vascular Surgery) , and in a few years it was expanded to 15 other hospitals, until in 1993 when the country's deep crisis brought about lack of the necessary material and gradual replacement of this method by RI. During all those years when hundreds of daily treatments were performed there was neither an

accident nor relevant second effect reported. We must also take into account the Italian experience: in the Congress of Verona (1999), Dr. Giuseppe Amato, a scrupulous physician who has always worked at the Hospital in Conegliano (Veneto), reported only one minor side effect without sequelae in thousands of patients treated with MO-AHT cycles for several years. The experience of Prof. Bocci at the Siena University Hospital is also significant: between 1995 and 2000, about 8000 MO-AHT were performed in patients with ARMD (age-related macular degeneration) and in approximately 100 patients with fibromyositis, as well as innumerable topical applications in chronic ulcers of the limbs, intradisc direct and indirect applications (oxygen-ozone infiltrations in paravertebral muscles) in about 80 patients with backache, etc.

Firstly, regarding second effects that may be produced during and after MO-AHT, in very few cases, almost exclusively in the first treatment, mild transient effects somewhat similar to hyperventilation (which can produce tingling sensation, cramps, dizziness, hot or cold sensations, muscle tension, weakness in the legs, blurred vision, palpitations, shivering, etc.), could arise, which makes sense, mainly in patients who start treatment in circumstances in which their bodies had already been adapted to insufficient oxygenation chronic conditions. It is well-known that MO-AHT application leads to a sensitive increase, though transient at the beginning, of arterial pO_2 arterial, thus being this the most likely cause of an apparent hyperventilation with the aforementioned initial transient effects. Likewise, in some cases, similar effect could be ascribed to lipothymy, very likely related to anxiety that the procedure causes in some patients, chiefly, when withdrawal and/or retransfusion take too long, due to low permeability of the vein or to a very high blood volume withdrawn causing certain hypovolemia effect.

During the 80's and early 90's the use of soft material bags for blood preservation in performing MO-AHT expanded to Italy and to some other country. During that time, certain second effects were often reported. For example, the very active team of Prof. Bocci, of Siena University, reported incidence of some effects such as tingling sensation on lips and tongue, nausea, stomach bloating, and metallic taste in mouth, tiredness, etc. There were even some episodes of erythematous skin rash, with itchiness, nausea, suffocations and slight hypotension.

In the year 2000 this very group reported, for the first time, that PVC soft bags for blood preservation, under ozone action could release particles and admixtures such as zinc stearate, zinc 2-ethyl hexanoate, presents in admixtures of PVC bags, plasticizers like phthalates together with lipoproteins and other admixtures of this type of PVC, that could be the cause for most side effects observed. Also, these bags contained excess of citrate-phosphate-dextrose (CPD) as anticoagulant which, for being excessive could cause effects of slight transient hypocalcemia, with undesirable second effects. From then on, they adopted the use of homologated and ozone resistant materials exclusively, subsequently reporting that:

“ALL OF THE ABOVE-MENTIONED SIDE EFFECTS HAVE DISAPPEARED, AND NO OTHERS HAVE APPEARED. MOREOVER, NO ALLERGIC-LIKE INTOLERANCE HAS BEEN OBSERVED”.

SOME TIME LATER THE USE OF NON-HOMOLOGATED PVC BAGS FOR MO-AHT WERE PROHIBITED BY THE MINISTRY OF HEALTH IN ITALY.

On the contrary, the most common effect among patients receiving MO-AHT is a feeling of wellness that usually increases with the course of treatment.

Nowadays ozone is widely used in orthopedic pathologies, particularly in the case of pains in the lumbar region, for which a gas mixture of oxygen-ozone is usually injected in detectable strategic points in the paravertebral muscles of patients. Bocci defines it by the term “chemical acupuncture” (Bocci, 1998a) and contributes with the reasonable explanation that ozone acts on local nociceptors and triggers an immediate and effective antinociceptive response (in approximately 2/3 of patients) through chemical mediators. While intradiscal direct injection of oxygen-ozone (to degrade the proteoglycans in herniated discs) must remain in the hands of orthopedists and neurosurgeons, many other physicians perform the indirect method or paravertebral infiltrations for treating pain.

Immediately after IM injection, ozone dissolves locally in water of the interstice and generates several ROS: if, in the first administration, ozone concentration is 20-25 µg/ml, the gas volume exceeds 10 ml and is promptly infiltrated, a very acute pain may cause a vagal hypertone (negative inotropic and chronotropic effects) and the patient can suffer transient lipothymy (bradycardia, hypotension, profuse perspiration, transient loss of consciousness, etc.). Hence, it is advisable to perform "chemical acupuncture" with the usual precaution and injecting the gas very slowly. It is also advisable to remind the patient that the pain is bearable and will only take a few minutes. In general, improvement of backache overpasses transient therapeutic pain, so achievement is satisfactory. With an adequate injection, the embolism risk by oxygen becomes null and only one case has been reported of subcutaneous bruising (Fabris et al., 2001). Direct intradiscal injection could present with some mild second effects but rarely a transient headache.

If ozone therapy is carried out properly, it does not tend to cause problems. However, the physician must be able to cope with any emergency with Vital Basic Support and have the usual medical resources available at the doctor's office (Cummins, 1994).

Moreover, ozone therapy also causes general positive second effects: approximately 3/4 patients, particularly those feeling depressed and asthenic, report a feeling of wellness and euphoria after some treatments as well as a more refreshing sleep; it is also observed, after certain age, an increase in the physical condition, stress decrease, better appetite, etc.

7.1. Ozone therapy with conventional treatments.

Before endeavoring ozone therapy, the physician must know all the medical history of the patient and the drugs in current use. Mattassi et al. (unpublished) have observed a sudden marked hypotension in patients treated with ACE (angiotensin-converting enzyme) inhibitors and that were subjected to a rapid reinfusion of ozonated blood. This effect may be due to the activation of the kallikrein-kininogen cascade, as reported by Shiba et al. (1997) and Abe et al. (1998). However plasma bradykinin is degraded within minutes and a very slow infusion reduces its adverse effect. Bocci confirmed Mattassi's observations in two patients, for which the following can be suggested in these cases: firstly, warn the patient on avoiding to take ACE inhibitors on the day of treatment with MO-AHT; and, secondly, slow down blood infusion and, thirdly, keep ready a vasopressive drug.

7.2. Contraindications for Ozone Therapy.

This is particularly important for systemic therapy in very specific cases where the risk of ozone therapy must be weighed against the clinical condition of the patient. Moreover, the following situations preclude or limit its use:

- (a) Patients with a significant deficit of G-6PD. Favism is a hemolytic disease observed in some people lacking this enzyme. This enzyme provides crucial reducing equivalents able to abolish excessive oxidation and intensive hemolysis (Chapter 4). On the other hand, Miller et al. (1993) after measuring the total antioxidant status in a great number of Europeans have founded stable values, excluding a significant depletion while ozone therapy. That is the reason why systemic ozone therapy is very well tolerated by the great majority of patients (Bocci, 2007a).
- (b) Pregnancy, particularly in the early phase, to exclude the mutagenic risk, although, according to the great number of preclinical studies in animals, it is very unlikely.

- (c) Abnormal situations with hyperthyroidism, thrombocytopenia, non-controlled coagulation disorders and serious cardio-vascular instability.

Last, but not less important, some years ago, in view of the need to elucidate the controversial issue on ozone toxicity, Prof. Bocci published an article titled very clearly: "Is it true that ozone is always toxic? End of dogma" (Bocci, 2006b). Doubtful strong reactivity of ozone and its toxicity for the respiratory system while prolonged exposure to polluted air, had contributed to establish the dogma that ozone is always toxic and, consequently, its use was avoided in medicine. Nevertheless, over the past 20 years, a clear understanding of ozone's action on biology and medicine has made clear that the dogma is not entirely true. It is vital to compare topography, anatomy and biochemical characteristics of organs exposed to ozone against the potent antioxidant capacity of blood exposed to a small and accurate ozone dosage for a few seconds. It is enough to recall that total surface of human lungs is approximately 70 m² and that the surface of the epithelial lining fluid (ELF) is only a thin fluid layer of up to 0,1 µm, thick thus total volume is only between 17 and 20 ml, absolutely insufficient to protect the alveoli from ongoing presence of air polluted by ozone.

Table 7.1 Comparison between ELF composition and blood in a person with common weight of 70 kg showing significant differences in antioxidant capacity between these two fluids.

	<u>ELF</u>	<u>Blood</u>
Volume:	17-20 ml	Plasma volume: 2.7 L Erythrocytes: 2.3 kg
Total proteins:	7 mg/ml (total: 130 mg)	Total plasma proteins: 75mg/ml (total: 202.5 g)
Albumin:	3.5 mg/ml (total: 63mg)	45 mg/ml (total: 121.5 g)
Transferrin:	0.3 mg/ml	2-4 mg/ml
Ceruloplasmin:	25 µg/ml	140-400 µg/ml
Lactoferrin:	0.5 µg/ml	?
GSH:	300-400 µM	In plasma: 3 µM In erythrocytes: 2.2 mM
Vitamin E:	2 µg/ml	10-20 µg/ml
Vitamin C:	3.5 µg/ml	9 µg/ml
Uric acid:	0.05 mg/ml	0.04 – 0.07 mg/ml
Glucose:	0.4 mg/ml	0.7-1.0 mg/ml
Total bilirubin:	?	1.0 mg/dl
Na: 82; Cl: 84; K: 29 mM		Na: 139; Cl: 103; K: 4 mM
pH	6.9	pH 7.4

? refers to an "unknown value"

This gas does not penetrate into cells, but dissolves easily and reacts with the thin fluid layer generating toxic molecules and causing inflammation, subsequently establishing in this way a vicious cycle with local and generalized damages. Undoubtedly, ELF, containing only a small amount of protective antioxidants is unable to neutralize ozone. (Table 7.1). Quite the opposite, both blood and extravascular fluids are made up of large volumes of fluids and contain a huge source of antioxidants and unsaturated fatty acids to neutralize a small ozone dosage. It is also enlightening to examine Fig. 7.1, which shows how the respiratory system, subjected to constant chronic inhalation of ozone releases a big amount of toxic compounds of the body so that this could explain why morbidity and mortality have risen in contaminated USA cities (Bell et al., 2005; Ruidavets et al., 2005; Jerrett et al., 2009). This article published in Toxicology and Applied Pharmacology has been object of many positive comments and it is expected that the issue of ozone toxicity has been clarified for good.

Chapter 8

Is Ozone really a "Wonder Drug"?

Ozone therapy has a tremendous therapeutic potential but so far gone unnoticed and

even blocked by the world's medical authorities. Among the reasons influencing underestimation of its usage, prejudices and subjective prevention against it, we can mention, on one side, ignorance of its specific characteristics as well as the very likely big pharmaceutical commercial interests against a therapy that may replace many highly consumed pharmaceuticals. On the other, it is also true that for many years ozone therapy has been developed empirically by private physicians, lacking resources and financing in order to organize basic studies. Fortunately in the 80's and 90's, some public institutions like the National Scientific Research Center of Cuba and the Siena University in Italy, began conducting this type of studies which have been basic in bringing ozone therapy to a more scientific level. It has also been very important the increasing endeavor of some European ozone therapy medical associations that have promoted congresses, courses and publications as well as numerous scientific research works, making possible to attract the interest of many other European public institutions.

Before analyzing the usefulness of ozone in several diseases (Chapter 9), we must sum up the number of biologic effects induced by this gas in the body after stimulation of blood, skin, subcutaneous cell tissue, muscle and gut lumen. Blood is obviously the best vehicle to transmit messages generated by ozone but other tissues have cooperative relevance.

Ozone therapy does not exclude orthodox medicine, but, in many cases it integrates into it. There are also vascular diseases such as chronic ulcers and wounds that do not undergo complete healing where ozone therapy is essential, whereas in other diseases it does not only play a useful role but also complementary.

Vasodilatation caused by the increase in release of NO, nitrosothiols (Joyner and Dietz, 1997; Kashiba et al., 1999) and autacoids can save ischemic areas in the limbs, heart, brain, kidneys and lungs. An increase in the supply and release of oxygen and nutrients is crucial in recovering seriously damaged cells, so that a timely ozone intervention can avoid irreversible injuries and likely death.

Release of a group of growth factors from platelets and endothelial cells can be responsible for extraordinary promptness with which ozone therapy produces healing of necrotic ulcers, particularly enhanced by topical application of ozonated water and oil.

Disinfectant properties of ozone on most pathogens are well-known, but, in Western countries, knowledge about therapeutic usefulness of ozone, especially in chronic infections (important abscesses, peritonitis, chronic osteomyelitis, etc.) is still minimal. How many thousands of patients with septic and toxic shock could have been saved if physicians had accepted to treat them vigorously with ozone therapy?

Despite from 1990 on the first ozone's effects on cytokine secretion such as NTF- alpha (Bocci and Paulesu, 1990) were reported, great deal of work still remains to do to fully understand the activation capacity and/or ozone's modulating effect in the immune system, after some months of ongoing therapy. Notwithstanding some evidence has been acquired about ozone therapy as a potent adjuvant for patients with hepatitis C, AIDS infections, multiple neoplasias, etc.

In the words of Prof. Bocci and other outstanding researchers in the field of ozone therapy: there are good reasons to affirm that prolonged ozone therapy can provoke four important phenomena:

- (A) Induction of oxidative shock proteins (OSP)
- (B) Increase of presence and activity of many antioxidant enzymes
- (C) therefore, reduction, if not normalization, of oxidative stress, and
- (D) likely release of bone marrow stem cells (BMSC)

With the current biological knowledge these are not preposterous ideas.

Regarding items (A) and (B), teleological importance of OSPs seems well demonstrated

in bacteria, fungi, plants and mammals. These results are really fascinating (Jolly y Morimoto, 2000).

Any change within external environment or in our internal milieu affects cellular homeostasis, but if the stress is bearable or adjusted in intensity, the cell can adapt itself and survive. If it were too violent, the cell programs its own death or apoptosis (Jacobson, 1996). A great number of stress types include hyperthermia, hyperoxia, hypoxia, ischemia, excessive production of ROS and LOPs, heavy metals, ethanol, hypoglycemia, pH modifications, viral, bacterial and parasitic infections, antibiotics, malignancy, radiation, metabolic and amino acid analogues inhibitors and very likely mental stress and hormonal disorder. Obviously, OZONE HAS TO BE INCLUDED: heat stress proteins (HSP70) are expressed after ozone inhalation (Su y Gordon, 1997) and attenuation of ozone-induced inflammation has been documented after repeated daily exposure (Christian et al., 1998). In relation to stress variety, the cell increases or synthesizes probably hundreds or more new proteins like HSPs (heat shock proteins), glucose regulated proteins (GRPs) and OSPs that allow the cell to resist against new and more intense types of stress. It has been observed than in the field of cytokines, there is an apparent redundancy with the final aim of establishing a "tolerance to stress" and ensure cellular survival. Paracelso (1493-1541) already had this intuition and in "Nature of Disease" he wrote that "the body possesses the art of destroying, but also of recovering health". Modern pharmacologic approach, though useful, can be too limited.

Future of ozone therapy relies on, partly, in OSPs, but it will be necessary to best demonstrate its relevance and scope. The concept is old and has been named in different ways, only because it has been observed under different pathologic conditions: Murry et al. (1986) were pioneers in the concept of "ischemic preconditioning" for the heart which after undergoing a brief and non-lethal period of ischemia has become more resistant to infarction from a subsequent ischemic insult. Goldman (1996) introduced the term "hormesis" to explain the "beneficial effect of a low level exposure to an agent which is harmful at high levels, e.g.: low doses of radiation induce an adaptive response to high doses in human lymphocytes (Olivieri et al., 1984; Wolff, 1996). Calabrese and Baldwin (2001) and Calabrese (2002, 2009) have presented a great number of examples of stimulating responses due to stimulus under the toxic threshold. This concept reflects Aristotle's thought (384-322 A.C.): "Principium quantitate minimum, potestate autem maximum", i.e.: minimal amount of drug (ozone) shows potent effects.

A kind of "oxidative preconditioning" has been achieved by means of warm ischemia or hyperthermia (Kume et al., 1996; Yamamoto et al., 2000), transient ischemia of the limb (Sun et al., 1999), MO-AHT (Bocci, 1996a, c). A number of studies controlled with ozone via RI and IP (intraperitoneal) routes in animals, which are much more simple and non-traumatic (León et al., 1998; Barber et al., 1999; Peralta et al., 1999, 2000; Borrego et al., 2004; Gonzalez, 2004; Madej et al., 2007) were able to demonstrate this oxidative preconditioning induced by ozone to a greater degree, protecting diverse organs against damages of a different nature. We are facing a real paradox since ozone, "the toxic gas", can turn into a useful therapy, capable of preventing and/or readjusting a chronic status of oxidative stress which otherwise would have been irreversible and deadly.

There are several pathologies such as arteriosclerosis, diabetes, ischemia, hyperhomocysteinemia, neurodegeneration, nephropathies, chronic viral infections, autoimmune diseases and cancer where there is a firmly established imbalance between oxidants and antioxidants, leading to a more or less rapid death. Currently we are also worried about obesity epidemic as a real sanitary risk factor.

How does modern medicine aim to correct this?

Let us consider, first, the strategies of our medicine to reduce oxidative stress in these diseases (Bocci et al., 2009). Due to a great variety of metabolic disorders we aim to:

- (1) Inhibit xanthine oxidase to reduce formation of superoxides and hydrogen peroxide using allopurinol (Farquharson et al., 2002).
- (2) Inhibit NAD(P)H oxidase (Lambeth, 2004). A direct action remains an unsolved

pharmacological problem and moreover there is a risk of increased bacterial infection.

- (3) Inhibit the renin-angiotensin system. Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin-II receptor antagonists are broadly used drugs for reducing blood pressure and interestingly they can also reduce oxidative stress by inhibiting NAD(P)H oxidase. On the other hand, Ca²⁺ channel blockers, beta blockers and alpha adrenergic receptor blockers are antihypertensive but do not improve the antioxidant status in patients (Baykal et al., 2003). Administration of diuretics can be coadjuvant but is transitory.
- (4) Inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is key enzyme for cholesterol biosynthesis. Currently in the market there are lipophilic and hydrophilic statins able to lower serum cholesterol levels, increase the number of LDL receptors and modulate psychopathologic processes in patients with acute coronary syndromes (Spencer et al., 2004). Statins have proven to be much more than agents to reduce lipids (Liao, 2002) because, by blocking the synthesis of critical isoprenoid intermediates, they express several other effects such as the inhibition of NAD(P)H oxidase, increasing the expression of endothelial NO synthase and of tissue-type plasminogen activator, while the expression of plasminogen activator inhibitor and endothelin-1 are inhibited. Therefore, multiplicity of hepatic and extrahepatic effects, by reducing inflammation, tumor progression (Katano et al., 2004) and an excessive immune reactivity (Vollmer et al., 2004) have raised statins at the level of "miracle drugs" comparable to penicillin (Roberts, 1996). Statins seem also able to mobilize bone marrow-derived progenitor cells (Llevadot et al., 2001) and practically every month a new beneficial effect is discovered. However, even with statins there are two problems: one is the cost limiting their use to a minority of patients (Topol, 2004) and the second is the danger of rhabdomyolysis. The risk is generally very low, but the administration of high doses of statins can cause this dangerous condition which forced the authorities to withdraw from the market a variant of these products, cerivastatin. In order to reduce the risk and to maintain the advantage of low cholesterol LDL levels, it was suggested to associate oral Ezetimibe with only 20–40 mg of statins daily. Ezetimibe inhibits intestinal absorption of cholesterol but even this combination does not appear totally safe because it may be a procarcinogenic stimulus and, therefore, the last suggestion would be to use Niacin instead of Ezetimibe.
- (5) Inhibit the excess of oxidants production by administration of either antioxidant vitamins or of a "healthy diet" enriched with polyphenols and flavonoids (red wine, olive oil, etc.). It is known that administration of compounds containing thiols (NAC and alpha-lipoic acid) can inhibit LDL oxidation. This seems a simple solution but, does ANTIOXIDANT ADMINISTRATION really works? This is a recurrent and fashionable theme, often dealt with by vitaminologists and folk healers, who may intoxicate patients with megadoses of selenium, zinc, iron and vitamins A, and E. Recognized scientists have often posed the question as to whether supplementation with antioxidants (Antioxidant therapy, AT) reduces oxidative damage in humans. The conclusion is that an equilibrated dosage may be essential during growth and useful in increased oxidative stress-related conditions, but there is little evidence that it can be a definitive remedy (Hennekens et al., 1994; Packer et al., 1997; Zino et al., 1997; Clinton, 1998; Halliwell, 1999a, b; McCall and Frei, 1999; Pryor, 2000; Polidori et al., 2001, 2004; Bender, 2002; Vivekananthan et al., 2003; Seifried et al., 2003; Ames, 2004; Victor et al., 2006). An excessive amount can modulate synthesis of HSPs and, indeed, reduce synthesis of HO-1 (Peng et al., 2000). If we deal with the problem realistically, we must consider:
 - a. the uncertainty of intestinal absorption;
 - b. the individual variability of metabolism and excretion;
 - c. the variable and normally reduced absorption of antioxidants by the cells;

- d. the possible reduced synthesis of GSH (observed in HIV infection);
- e. the potential toxicity of excessive doses;
- f. the inability of antioxidants to stimulate synthesis of antioxidant enzymes;
- g. the inability of antioxidants to inhibit this process.

Therefore, the problem of antioxidant supplementation must be seriously considered and while it could be useful and if the adequate and balanced amount is administered, it cannot make miracles.

- (6) Inhibit production of superoxides by long-term administration of L-arginine (Enwonwu, 1989; Morris et al., 2000), which is the substrate for NO synthesis.
- (7) Inhibit the excessive production of superoxide by SOD mimetics (Fontana et al., 1999), because the administration of an exogenous enzyme, unable to enter into a cell, has proven to be useless. Induction of SOD by gene transfer is still a possibility difficult to make concrete.
- (8) Inhibit the increase of homocysteine levels in the plasma because the autooxidation of its sulfhydryl group generates superoxide and hydrogen peroxide that can become cytotoxic for the endothelium. Hyperhomocysteinemia can be controlled by administration of folic acid plus vitamins B6 and B12 (Das, 2003) and by an increase in plasma level of adenosine (Riksen et al., 2003).
- (9) Inhibit platelet aggregation with aspirin, clopidogrel, ticlopidine or the like.
- (10) Inhibit the synthesis of pro-inflammatory autacoids by the daily administration (2 g) of n-3 PUFAs present in fish oil, which enhance the generation of 3-series PGs and 5-series LTs, which are anti-inflammatory (Belluzi et al., 1996; Mori et al., 2003).
- (11) Inhibit hyperglycemia by carefully regulating caloric intake with abundance of fresh vegetables and adopting a proper life style without smoking as well as making the time for, at least, 30 min of moderate physical exercise (Fontana et al., 2004).
- (12) Inhibit inflammation by using corticosteroids and non-steroidal anti-inflammatory drugs (NSAID). Both types of drugs can be used for a limited time owing to their usual adverse effects.
- (13) Inhibit the formation of advanced glycation end-products (AGEs). These toxic compounds deposited in arterial walls may induce an oxidative stress and speed up progression of Type 2 diabetes, atherosclerosis, renal and retinal damages. Hyperglycemia and obesity and improper life style must be intensively controlled.

We have summarized the most relevant therapeutic strategies offered by our medicine to reduce oxidative stress: except for statins and anti-hypertensive agents, the use of them separately has little meaning and cannot solve the problem. Even if it implies taking six or more tablets, this cocktail type therapy at long-term is recommended despite its cost. If the patient follows treatment, the real evidence is that morbidity and mortality of really ill patients will prove significantly reduced suggesting that this multiform treatment can slow down involution.

Does it make any sense recommending ozone therapy? Ozone, perhaps, cannot eliminate primary causes of these diseases, but is very capable of reversing chronic oxidative stress.

Can ozone stand-alone do as much as all the aforementioned treatments? So far, it has been able to reduce oxidative stress in all studies undertaken in many different pathologies and, at least, initially, it would be wise to consider ozone therapy as an integrative support.

A transient ozone treatment with its oxidative stress calculated brings about a "slight therapeutic shock" for the organism in crisis. Ozone makes this shock because it generates a

number of messengers that can reach all cells of the organism. How can this happen? First, it is necessary to distinguish between local and parenteral treatments. In the latter, MO-AHT is reasonable accurate and either hydrogen peroxide or, especially, the LOPs it generates with a longer half life are the most important agents of ozone's effects. Therefore, during and immediately after one of these treatments, the cells throughout the body will receive a new pulse from LOPs and generated autacoids. As it was mentioned in Chapter 4, these compounds are heterogeneous and suffer a dilution and metabolism (Vasiliou et al., 2000). At a certain level, they could be cytotoxic, while under low micro-levels or nanomolar ones (those provided by ozone therapy) can react as physiologic messengers through interaction with several cell enzymes (Forman et al., 2008) and is a good reason to start with ozone therapy in the lowest part of the "therapeutic window", and to scale progressively. One possible way to interrupt the cell "anergy" due to chronic oxidative, can be adequate atoxic stimulation of the cell by some molecules of LOPs, generated by ozone therapy, which may achieve functional recovery, as stated in studies published about degenerative diseases of the CNS as well as in the recovery of the "shadow" zones after vascular accidents. If the cell is capable of transducing the message to the nucleus via kinase phosphorylation and similar, may represent the warning sign that reactivates the gene expression thus provoking synthesis of OSPs and antioxidant enzymes. While a high concentration of LOPs or a very advanced disease will end with cell death, a low and gradual stimulation as this one may enhance reequilibrium of the oxidant-antioxidant balance. If the idea is right, ozone therapy should start with concentrations just above the therapeutic threshold. Laboratory experiments with animals (León et al., 1998; Barber et al., 1999; Peralta et al., 1999, 2000; Borrego et al., 2004; Stadlbauer et al., 2008) daily treated by RI or by intraperitoneal insufflation with a controlled ozone treatment have demonstrated an amazing adaptation to chronic oxidative stress with the subsequent resistance to prolonged ischemia and to toxic compounds or minor rejection to allograft. Fig. 8.2 shows response of a patient with MDRA (age-related macular degeneration) to one MO-AHT and the subsequent treatment cycle.

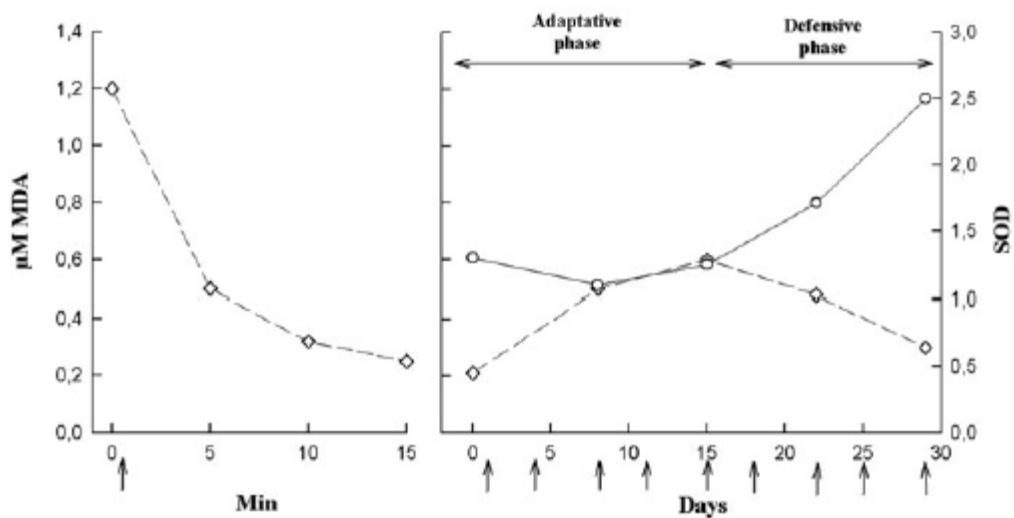


Fig. 8.2 Response of a patient with ARMD (age-related macular degeneration) to only one infusion (left graph) or intermittent infusions (right graph) of MO-AHT (300 g of blood treated with one ozone dose of 21 mg/session). MDA, malondialdehyde (♦) y Mn-SOD (U/ml plasma) are presented in the ordinates. Arrows indicate the moment of treatment. (Bocci, 2002)

What proteins and enzymes are important in correcting chronic oxidative stress? This issue has been researched extensively over the past 15 years and it has been demonstrated that hyperoxia and ROS can induce high levels of SODs, GSH-Pxs, GSSGR and catalase (Heng et al., 1987; Rahman et al., 1991; Shull et al., 1991; Doroshov, 1995; Hernandez et al., 1995; Bocci, 1996a; Tacchini et al., 1996; Sagara et al., 1998; Wang et al., 1998; Barber et al., 1999; Chen et al., 2000; Csonka et al., 2000). All these data has been encouraging in proving the effects of ozone therapy.

Ongoing research is conducted on levels of antioxidant enzymes, G-6PD (Puskas et al., 2000) and some inducible oxidative shock proteins by hydrogen peroxide and ozone (Jornot et al., 1991; Cardile et al., 1995; Kiang y Tsokos, 1998), before, during and after ozone therapy.

It is interesting to analyze the HO-1 (or HSP-32) pattern because even a subtle exposure of blood to ozone (40 µg/ml) seems to release traces of the heme-group. This decomposition generates beneficial molecules such as traces of CO acting synergically with NO as vasodilator, bilirubin acting as lipophilic antioxidant (Abraham et al., 1996), as well as free Fe²⁺ that, if not rapidly chelated, can act as a pro-oxidant (Dong et al., 2000; Nath et al., 2000; Rytter and Tyrrell, 2000; Snyder and Baranano, 2001). In short, HO-1 is becoming the most interesting enzyme (Galbraith, 1999; Zuckerbraun and Billiar, 2003; Bocci et al., 2007), involved in cutaneous protection (Reeve y Tyrrell, 1999), in prevention of hematic toxicity and iron oversaturation (Nath et al., 2000), in suppression of endothelial cell apoptosis (Brouard et al., 2000), in blockade of vascular growth of smooth muscle cells (Durante, 2003), in rejection of cardiac transplantation in mice (Sato et al., 2001) and in protection of the heart, liver, kidneys and lungs against ischemia/reperfusion (IR) and damage by hyperoxia (Csonka et al., 1999; Amersi et al., 1999; Otterbein, 1999; Miyazono et al., 2002; Choi et al., 2003; Wagner et al., 2003; Seixas et al., 2009).

Antioxidant supplementation regime with NAC can be maintained during ozone therapy, but it is very likely that, unless we are able to ACTIVELY increase the intracellular enzymatic antioxidant capacity, even if corporal fluids are saturated with exogenous antioxidants, there is no hope to repair the cell and reach a therapeutic outcome.

Ozone can be a good alternative or even better than the previously mentioned treatments and what should be essential is to compare the different treatments in a randomized clinical trial. This task is certainly impossible with our means and conventional medicine is not going to spare time on this since statins are a big "business". For the time being and for the sake of the patient, at least, we can suggest acceptance of the usual therapy associated with the less invasive ozone therapy to obtain a maximum effect with minimum discomfort.

The final point deals with the exciting possibility to enhance oxygenation of ischemic tissues by promoting angiogenesis. It has been demonstrated that autologous mononuclear bone stem cells (BMSC) and/or endothelial progenitor cells (EPC) can play a role in speeding up angiogenesis of human myocardium, thus improving perfusion of infarction zone and then leading to regeneration of this zone (Strauer et al., 2001; Orlic et al., 2001; Schwartz and Curfman, 2002; Aicher et al., 2003).

First we must consider that conventional medicine has attempted to sort out this problem. Two approaches have been used: The first consists in withdrawing autologous BMSC and transplanting them via intracoronary or transendocardial routes. Invasiveness of method may limit its clinical application. The second method resorts to release of SC in circulation after administration of stimulating factor of granulocyte colonies (G-CSF). After withdrawal of hematopoietic stem cells (using CD34 as marker for SC) from circulation, they are infused via intracoronary route. This method is relatively practical, but there is the risk of re-stenosis (Kang et al., 2004). Therefore, though both routes improve myocardial perfusion, do not seem to be the ideal procedures.

Ozone therapy can be advantageous because it promptly improves oxygenation and the ischemic tissue metabolism, being able to mobilize endogenous SC thus avoiding cell extraction and transfusion. Hypothesis that ozone therapy can improve release of SC from bone marrow was proposed a while ago (Bocci, 2002) to explain the astonishing long-term remission in two of seven cardiopathic patients, after ozone treatment when the normal therapeutic effect only lasts for a few months. It was obvious to imagine that some type of healing or myocardial restoration could have occurred if the BMSC reached the infarction zone and regenerated, at least partly, but unfortunately a proper assessment was not able to be conducted.

Even if localization of SC remains elusive, seems that every organ (liver, brain, skeletal muscle, skin, endothelium and also cancer) has been endowed of these cells, but the real treasure, seemingly, is that the bone marrow contains approximately 1% of hematopoietic cells and approximately 0.05% of mesenchymal stem cells (CMM). It has been demonstrated

(Barakat et al., 2004) that in rats, after an intraperitoneal ozone injection of variable concentrations (4.0, 40.0 and 75.0 µg/ml), induction of neoangiogenesis can be achieved, in skeletal muscles as well as in the cardiac one with mean ozone concentration. If this occurs during prolonged ozone therapies, it has not been determined yet. However it is one of the most exciting possibilities for research. After all, almost every day, we realize of faster healing of cutaneous ulcers in patients with chronic ischemia of limbs subjected to ozone therapy which can reflect cardiac improvement.

The idea that ozone therapy can mobilize the BMSC is supported by some biochemical data: several years ago, LOPs present in ozonated human plasma were demonstrated to induce NO synthetase (NOs) in endothelial human cells and significant release of NO and nitrosothiols were measured (Valacchi y Bocci, 2000). These compounds have a key importance in physiology of vascular bed since it improves vasodilatation and inhibits platelet-leukocyte adhesion and muscular cell proliferation (Joyner and Dietz, 1997; Kashiba et al., 1999; Stamler, 2004). Aicher et al. (2003) have added the crucial discovery that induction of endothelial NOs is essential for neovascularization, since NO activates the metalloproteinase-9 (MMP-9) matrix which is indispensable for mobilizing the SC

As conclusion, this process can be distinguished in four phases:

- i. MOBILIZATION or RELEASE of BMSC, MSC and EPC (meaning or list of acronyms at the beginning). Reinfusion of ozonated blood represents an acute, accurately calculated stress able to stimulate the bone marrow by means of LOPs and possibly autacoids, growth factors and cytokines. The sudden homeostatic change in the bone marrow microenvironment caused by these messengers (particularly NO) may well be an effective way for enhancing the output of stem cells.
- ii. THE JOURNEY TO THE TARGET: circulatory BMSC, MSC and EPC do not get lost in the vast expanse of the vascular bed and eventually home in an injured site that likely is an ischemic and/or an infarcted area.
- iii. HOMING may be determined by chemoattractant mechanisms as damaged tissues may release chemoattractant factors or express new receptors where SC can dock.
- iv. INCORPORATION and TISSUE REPAIR, given due time, can occur via proliferation and appropriate differentiation of SC, thanks to improved oxygenation and presence of growth factors in the microenvironment. If this is correct, even a small number of SC can be eventually sufficient to reconstruct the infarcted zone.

Although we humans have not the power to regenerate the organs, except the liver, the present state of the art is encouraging for the heart and can also help to spare amputations of limbs in some patients. An astonishing result observed in one patient at the 4th stage of POAD after ozone therapy has led us to believe that only the new formation of an efficient circulatory network could have allowed the recovery from an apparently irreversible damage. However, highly compromised patients with advanced dysmetabolic syndrome appear unable to recover. There can be little doubts that, besides a correct timing and efficacy of the therapy, genetic, metabolic and neuroendocrine factors play an important role in the final outcome because only a minority of patients in stage 4 has a positive response. Results obtained with prostanoids' infusion are inferior to those of ozone therapy (Di Paolo et al., 2005) suggesting that ozone deserves to be thoroughly examined. It will not be easy but it is worthwhile to research with refined instrumental analysis if this repair process really occurs in vasculopathic patients treated with ozone therapy. If ozone therapy really offers an advantage over the more elaborate administration of stem cells via special routes (Strauer and Kornowski, 2003), it ought to be seriously researched because we could easily and inexpensively help a far larger number of critical patients.

A final observation regards the duration of ozone treatment and if it allows "curing" a disease. Around 80 A.D. Tacitus wrote "nature infirmitatis humanae tardiora sunt remedia quam mala" or, "on the basis of the nature of human frailty, remedies work more slowly than illnesses". This remains true today for both orthodox medicine and ozone therapy. With this complementary approach it takes some time to notice a real improvement and this greatly

depends on the status of the patient, age, type of disease, the quality of the treatment and also on the competence of the physician. Moreover ozone therapy is mostly applied to diseases regarded as incurable and, precisely, due to this, and to frustrations suffered with conventional medicine for a long time is why many patients turn out to it. In many cases, ozone therapy can, at least, correct or block its progression and in other cases this benefit can be kept over time with a maintenance therapy.

Chapter 9

The Clinical Applications of Ozone therapy.

Clinical results available so far have demonstrated that ozone therapy is often as useful or more than usual treatments in a FIRST category of diseases such as:

- (1) Osteomyelitis, empyema pleural, abscesses with fistulae, infected wounds, ulcers by pressure, chronic ulcers, diabetic foot and burns (Payr, 1935; Aubourg, 1940; Rokitansky, 1982; Miroshin and Kontorshikova, 1995; Werkmeister, 1995; Shaschova et al., 1995; Filippi and Kirschner, 1995; Wasser, 1995a; Bulinin et al., 1995; Kudravcev et al., 1995; Kasumjan et al., 1995; Steinhart et al., 1999; Valacchi et al., 2005; Travagli et al., 2009a; Menendez et al., 2010).
- (2) Advanced ischemic diseases (ischemia of the lower limbs and the heart, sequelae of encephalic and cardiac vascular accidents, also possibly cardiac attack when patients get too late for thrombolysis) (Rokitansky, 1981, 1982; Romero et al., 1988; Amato, 2000; Giunta et al., 2001; Tylicki et al., 2001, 2003, 2004a, b; Biedunkiewicz et al., 2004; Di Paolo et al., 2005; Clavo et al., 2011).
- (3) Senile macular degeneration (atrophic form), because ophthalmology does not count on a significant treatment yet (Riva Sanseverino et al., 1990; Bocci, 2002; Borrelli and Bocci, 2013).
- (4) Neurodegenerative diseases such as: dysfunctions of the optic nerve, retinitis pigmentosa, open angle primary glaucoma, senile dementias including Alzheimer, cerebrovascular ischemic disease cochlear-vestibular syndrome, etc. (Rodríguez, García, et al. 1998; Rodríguez, Menéndez, Devesa, et al. 1998; Rodríguez, Menéndez, García, et al. 1998; Copello et al., 2003; Copello et al., 2013).
- (5) Degenerative and inflammatory orthopedic diseases (osteoarthritis, etc) (Riva Sanseverino, 1989; Verga, 1989; Siemsen, 1995; Bocci et al., 2000; Jucopilla et al., 2000; Alexandre et al., 2000, 2002; Bonetti et al., 2001; Fabris et al., 2001; Petralia et al., 2001; Tabaracci, 2001; Andreula et al., 2003).
- (6) Chronic fatigue syndrome and fibromyalgia (Cosentino et al., 2000; Loconte, 2000; Borrelli and Bocci, 2002; Hidalgo-Tallón et al., 2012).
- (7) Lesions in dental roots due to cavities, especially in children (Baysan et al., 2000).
- (8) Dentistry: Chronic and recurring infections in mouth cavity (Lynch, 2004).

Also in a SECOND category of diseases including:

- (1) Acute and chronic infectious diseases, especially those implying bacteria, viruses and fungi, chemo and antibiotic resistant (hepatitis, HIV-AIDS, herpetic infections and herpes zoster, infections by the papillomavirus, onychomycosis, candidiasis, giardiasis and cryptosporidiosis) – ozone therapy seems a useful support (Mattassi et al., 1985; Bocci and Paulesu, 1990; Konrad, 1995, 2001; Bocci et al., 1998c; Amato et al., 2000; Mawsouf et al., 2004; Bocci et al., 2009b).
- (2) In fatigue by cancer and tolerance to chemotherapeutic drugs, ozone therapy associated to habitual treatments have demonstrated (Clavo, 2004b) its

usefulness because it improves the quality of life and decreases the adverse effects related to chemo and radiotherapy.

Finally there is a THIRD category of serious diseases such as:

- (1) Autoimmune diseases (rheumatic diseases, psoriasis, Crohn's, etc) (Menéndez et al., 1989; D'Ambrosi, 2002b; Esperanza, S., Ortellado, M., 2011; Molinari et al., 2014).
- (2) Senile dementia (Rodríguez et al., 1998).
- (3) Pulmonary diseases (emphysema, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and acute syndrome of respiratory difficulty) (Hernandez Rosales et al., 2005; Bocci, 2007b).
- (4) Cutaneous diseases (psoriasis, Stevens-Johnson Syndrome and atopic dermatitis) (Abeck and Plötz, 2008; Borrelli et al., 2008; Izzo, 2008; Menendez et al., 2010; Sirito, 2006; Travagli et al., 2009a, b, 2010c; Zamora et al., 2008; Re et al., 2015).
- (5) Metastatic cancer (Akbarov et al., 2010).
- (6) Severe sepsis and dysfunction of multiple organs (Bocci and Brito, 2006).

in which combination of orthodox treatments and ozone therapy is, at least in theory, useful, though more official clinical trials are needed that could be carried out promoting cooperation among Ozone Therapy Scientific Societies and Non-Profit Private and Public Health Institutions. If ozone therapy with its low cost and no side effect advantages may equal efficacy of current conventional treatments, it deserves to be more thoroughly researched. We must take into account that all results, clinical and preclinical evidences, reasoning and arguments stated have been developed with praiseworthy efforts despite lack of specific sponsors. Surprisingly, developing countries, like Cuba and China, with lower health budgets have been and continue carrying out a number of clinical studies contributing with a valuable information regarding usefulness of ozone therapy.

National authorities of the health system who are always coping with cost rises in medical assistance and budget constraints could obtain a very significant assistance and economic advantage if ozone therapy were extended to and systematically organized at all public hospitals. Though we may not count on data enough to quantify the benefits from ozone therapy, with its low added cost, we are convinced that they can contribute to a very important decline in marketable medications consumption and avoid very expensive procedures, such as surgical ones and others; reduction of recovery periods and less losses by disease, better quality of life, etc., in all the categories of diseases already mentioned.

The WFOT will edit guide-lines for different diseases according to the evidences, as soon as enough publications support them.

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