

Alhamdulillah

in the name of god



Ozone therapy

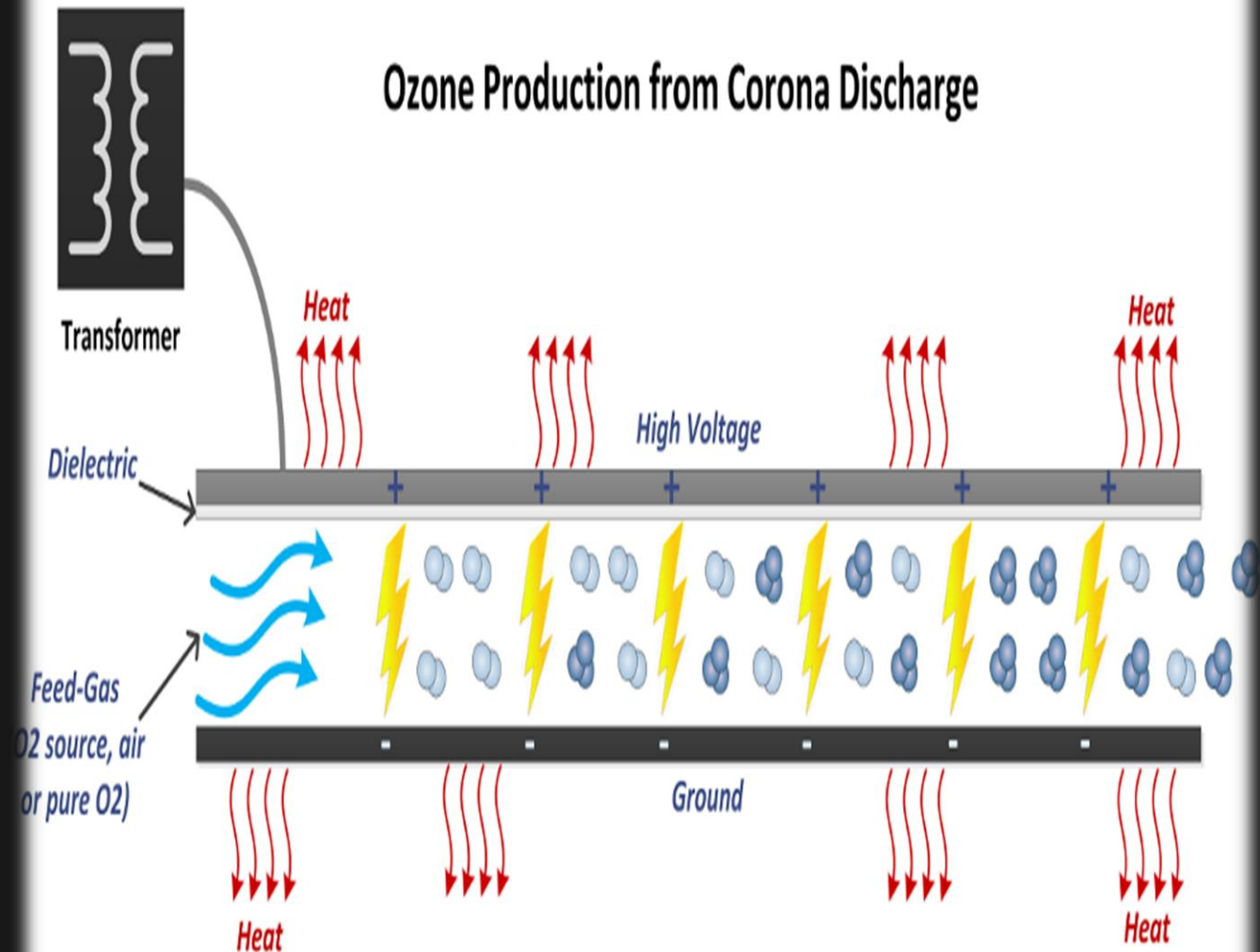
in

Pain & Palliative Medicine

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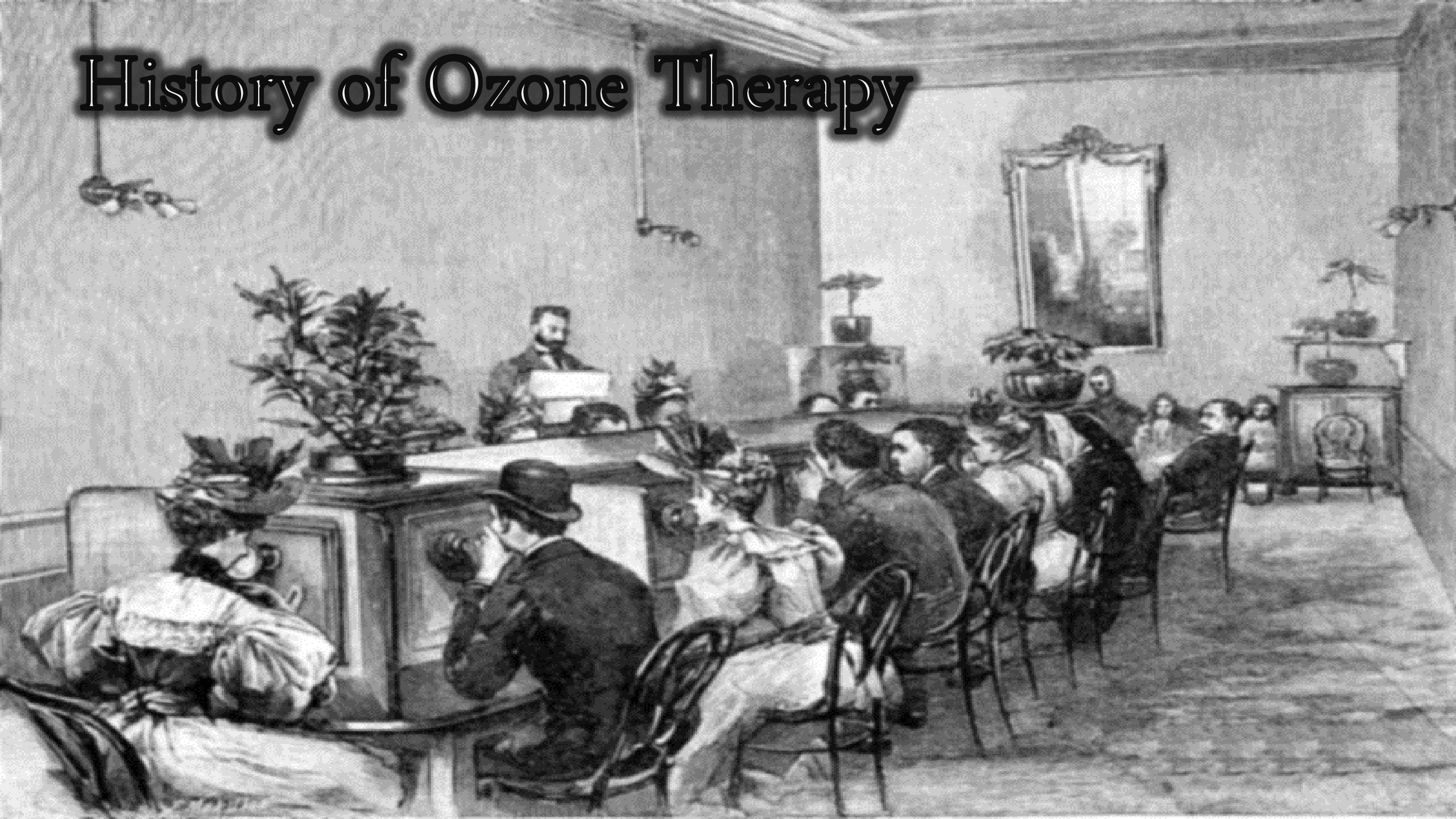
- ❖ **Ozone (O₃)**, a gas discovered in the mid-19th century and composed of three oxygen atoms
- ❖ It exhibits **high solubility** in plasma, extracellular fluids, and water (approximately **10 times more soluble** in water than oxygen)
- ❖ **At room temperature**, it is **unstable**
- ❖ Notably, its half-life measures 25 minutes at 30°C, 40 minutes at 20°C, and 140 minutes at 0°C

- ❖ It cannot be stored and must be produced "in situ"
- ❖ The gas is colorless, acrid in odour and explosive in liquid or solid form
- ❖ Medical ozone is a blend of oxygen and ozone derived from medical-grade oxygen through the utilization of a medical ozone generator.
- ❖ Only 3% to 5% of this gas coming out of the generator consists of ozone, the rest is oxygen.



Ozone is formed via an electrical discharge that is diffused over an area using a dielectric to create a corona discharge. Oxygen passed through this corona discharge is converted to ozone.

History of Ozone Therapy

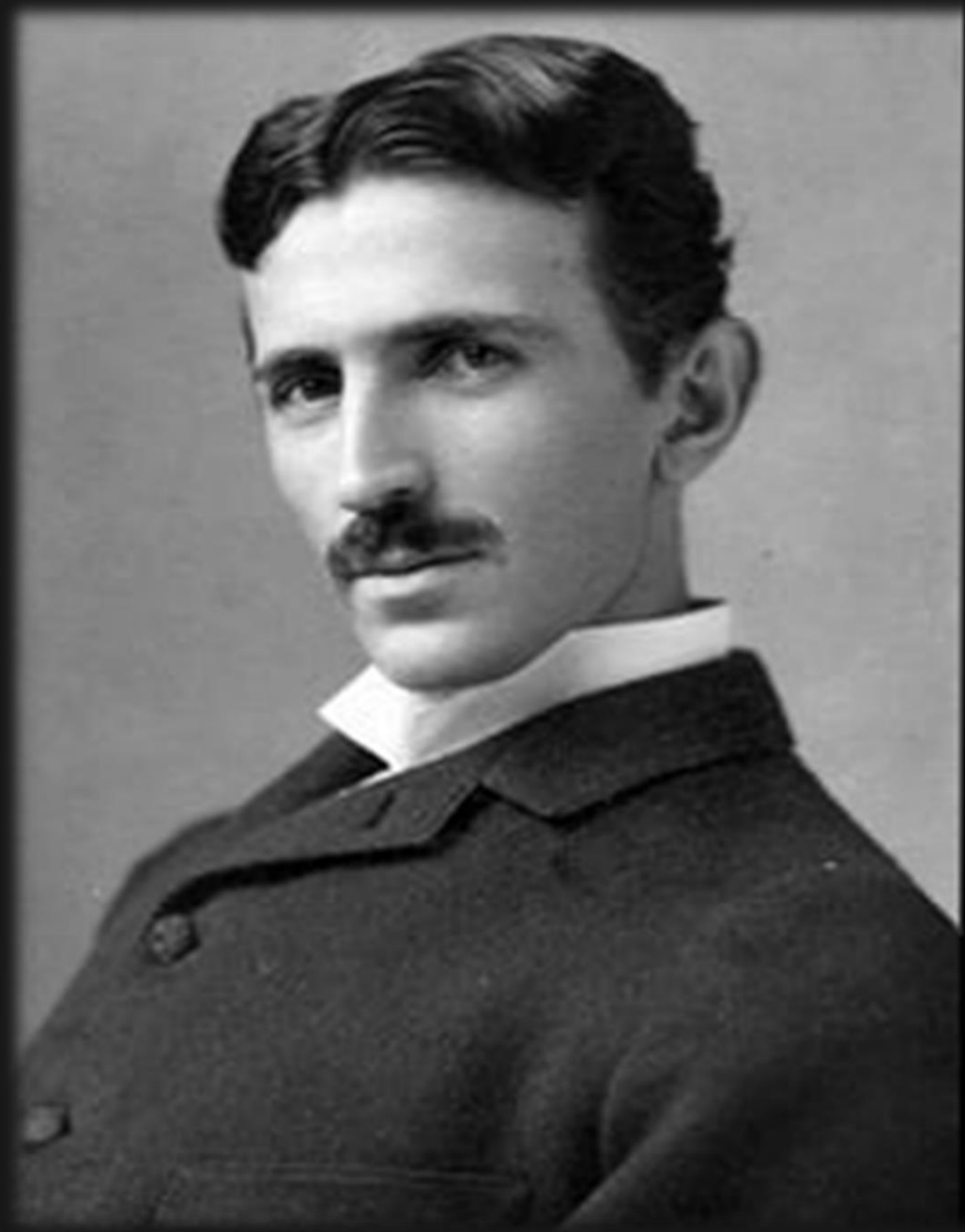




OZONE DISCOVERY

Christian Friedrich Schönbein

Schönbein's ozone discovery occurred in the late 1830s, while he was doing experiments on the electrolysis of water. He noticed a distinctive odor, similar to the smell following a bolt of lightning. In 1839 he succeeded in isolating the new chemical substance and named it from the Greek word "ozein," meaning "to smell."



- ❖ 1914 - During the World War I (1914-1918) ozone was used to treat wounds, trench foot, gangrene and the effects of poison gas.
- ❖ 1915 - Dr. Albert Wolff uses ozone to treat colon cancer, cervical cancer and decubitus ulcers, in Berlin.
- ❖ 1930 - A Swiss dentist Dr. E.A. Fisch was using ozone in dentistry
- ❖ In the late 1980s, reports had emerged that German physicians were successfully treating HIV patients with O₃-AHT (Autohemotherapy).
- ❖ 2001 - Ozone is approved by the FDA as a secondary direct food additive, antimicrobial agent.
- ❖ 2019 - Systemic ozone therapy can be "potentially" useful in SARS-CoV-2.

Why Ozone

Instead of Oxygen?

- ❖ Oxygen is a more stable element than O₃.
- ❖ The solubility of O₃ in biological fluids is 10 times higher
- ❖ Therefore, the risk of embolism is less than oxygen.
- ❖ O₃ is an unstable molecule, it enters chemical reactions more easily. It is more effective in creating a biological response.
- ❖ O₃ is called active superoxygen because of its effects
- ❖ An effective, safe, feasible, and easy-to-perform technique in various inflammatory, infectious, degenerative diseases, as well as in rehabilitation following acute cardiac and cerebral ischemic events

- ❖ Good efficacy both as an independent treatment and, notably, as an adjunct to conventional therapies
- ❖ Combined with standard therapies, it often leads to reduced medication dosages, complication rates, treatment duration, medication toxicity, and medical expenses

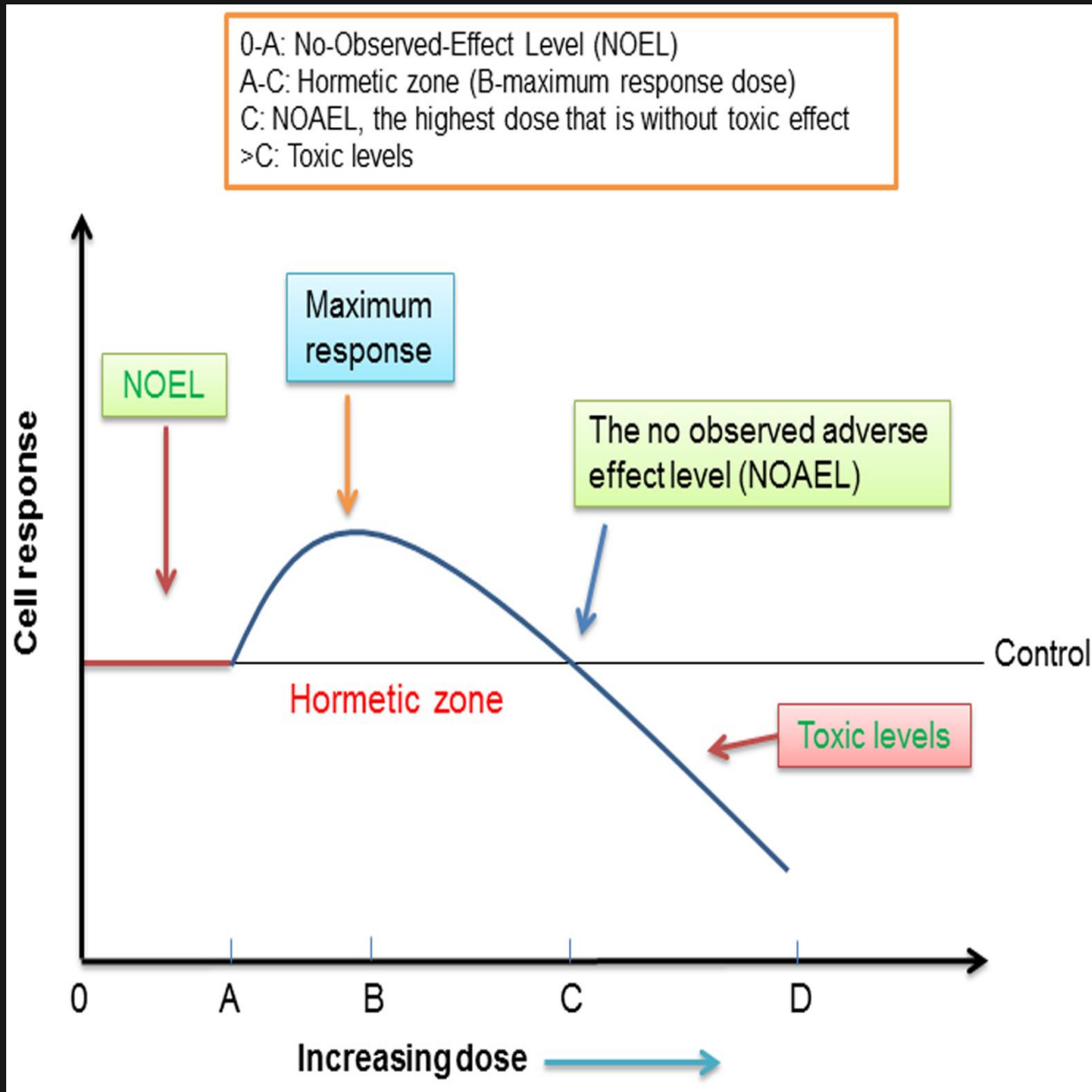
molecule of Ozone

How Does Ozone Act?

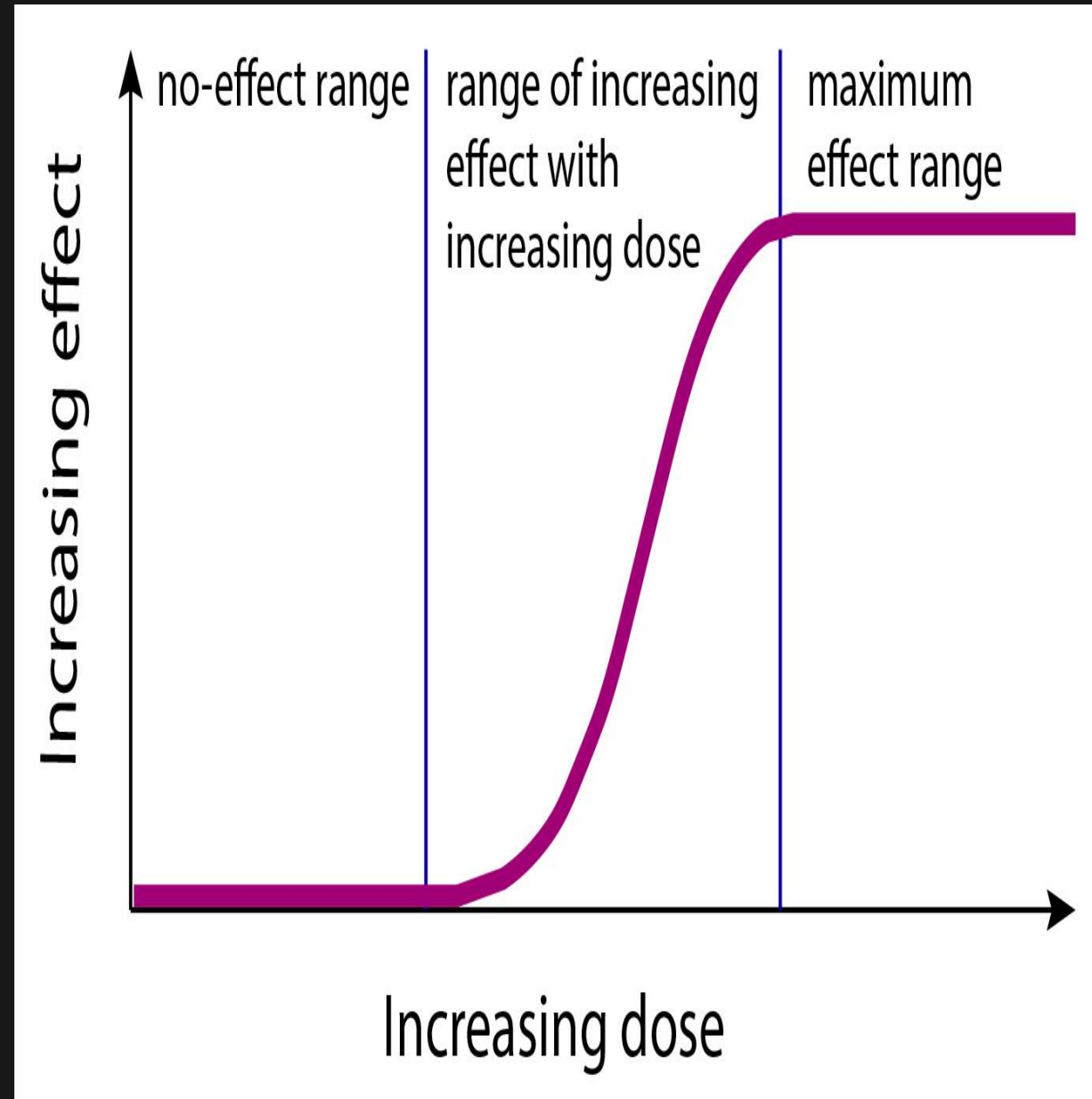
O₃



Hormetic Effect



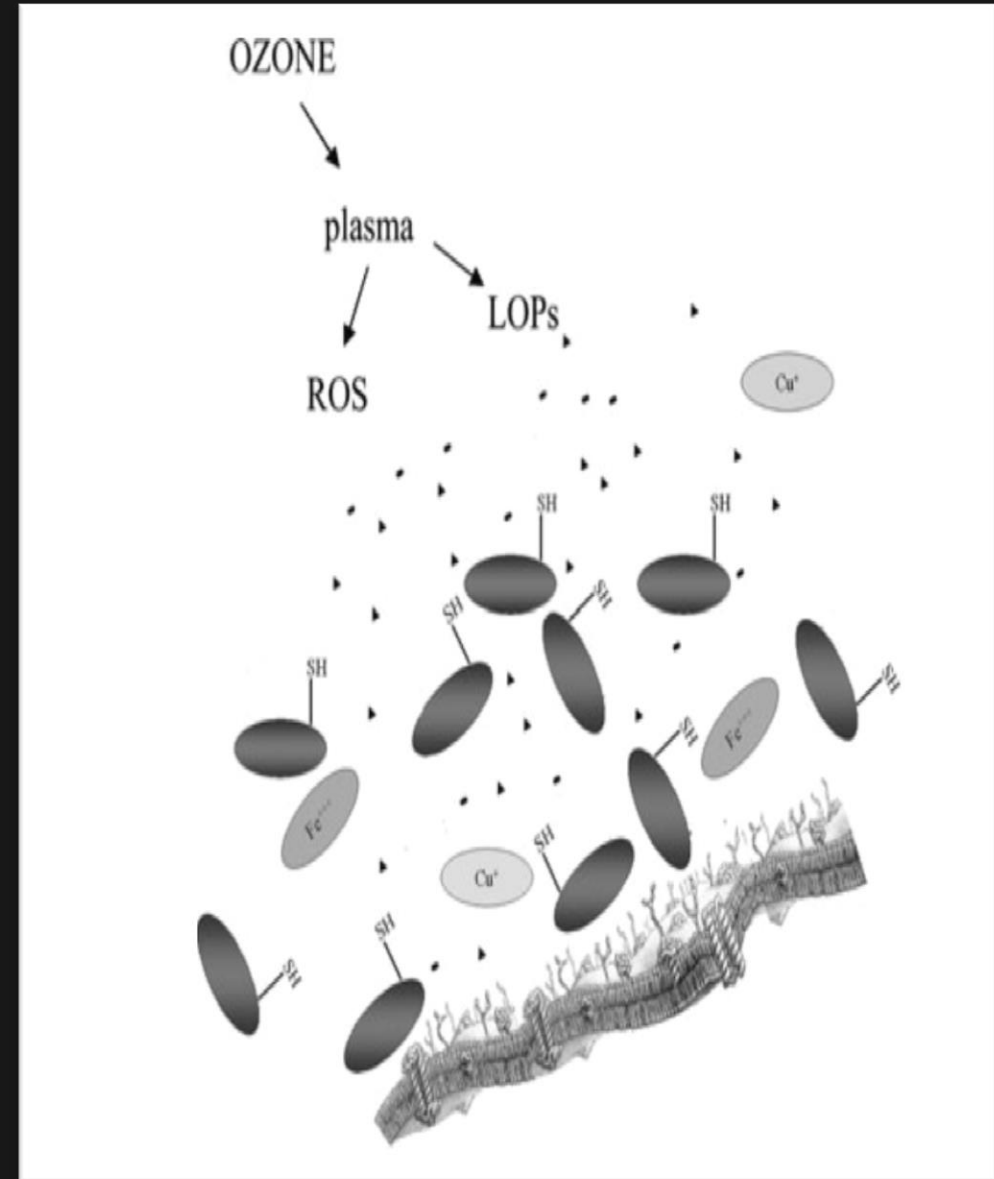
Dose-Response Curve



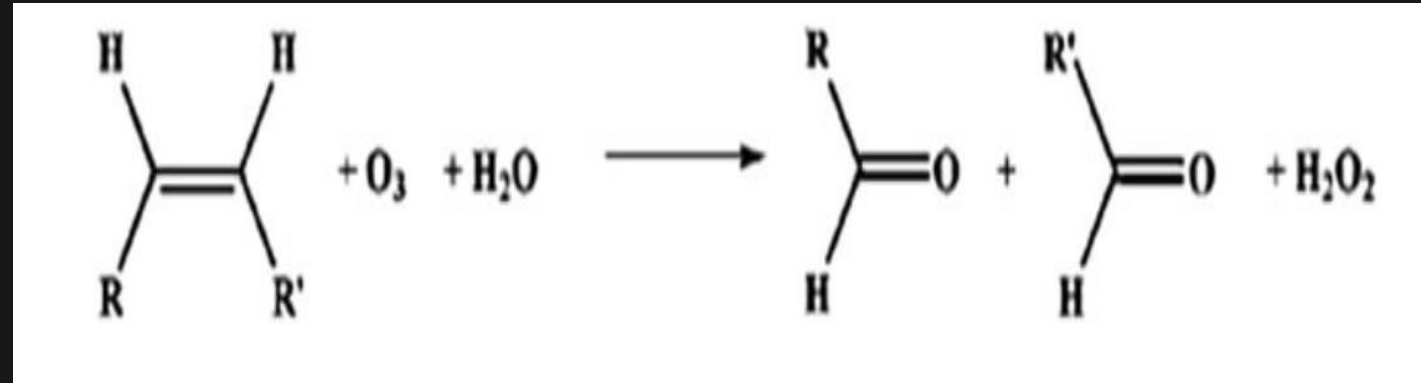
- On the contrary to what happens for a simple receptor interaction, reactions induced by stress require the introduction of a third parameter vector in addition to the DOSE and the EFFECT:

That is the Time

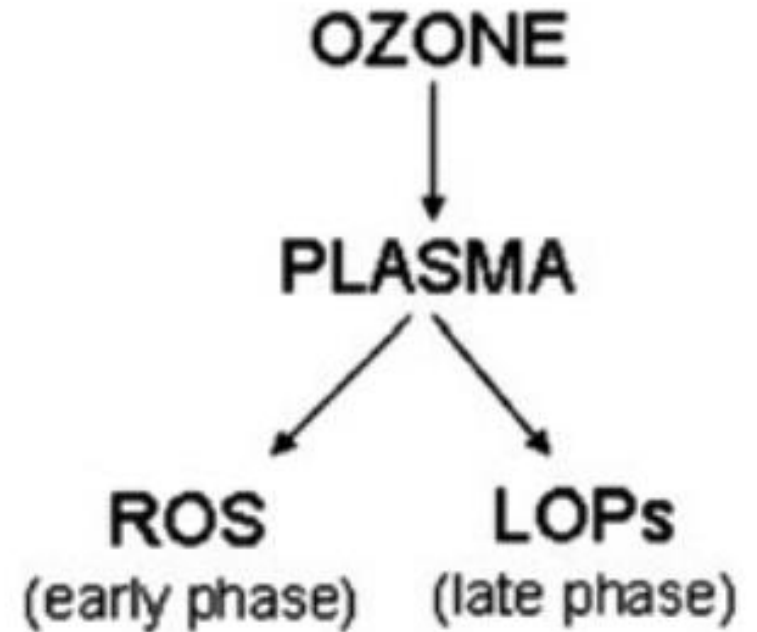
- Ozone is an **unstable gas** that shows a **high reactivity** towards biological substances.
- Among these are included proteins, amino acids and unsaturated fatty acids, which form part of the composition of the lipoprotein complexes of plasma and of the double layers of the cellular membranes.



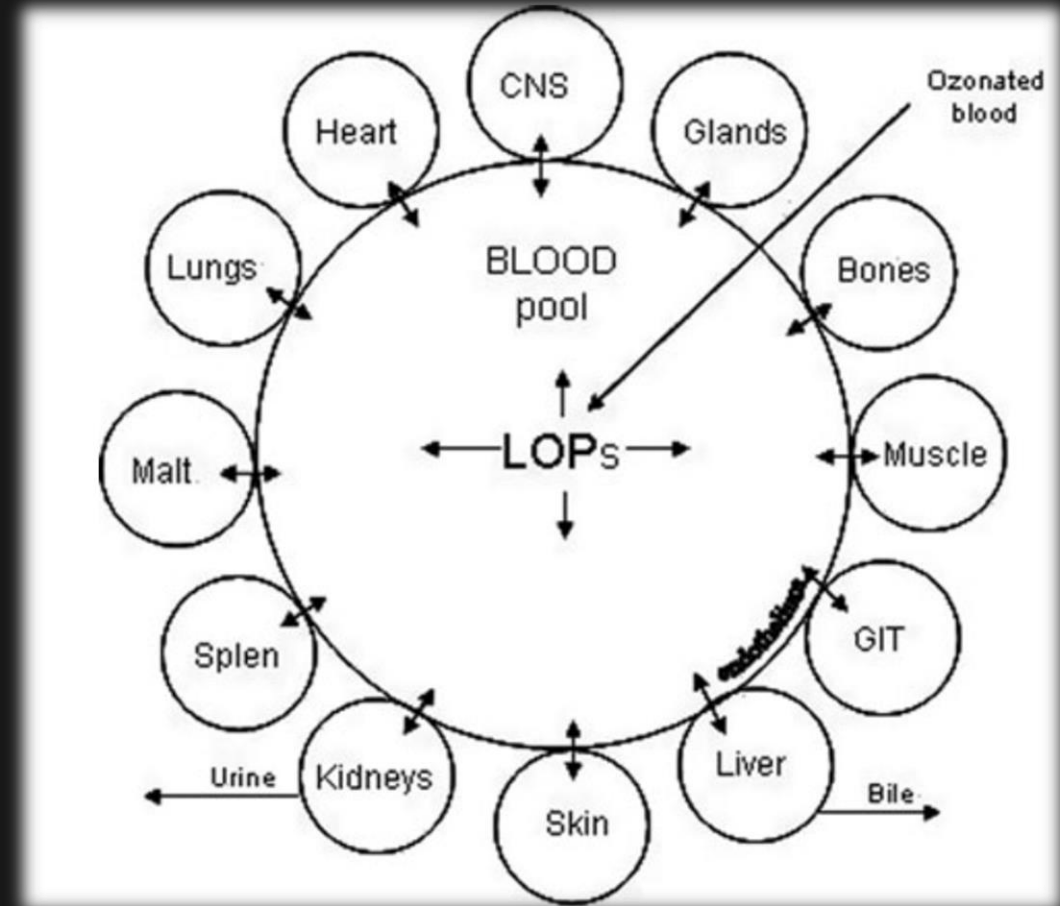
LIPID PEROXIDATION



From now on, ozone is exhausted and only **ROS** (mostly hydrogen peroxide) and **LOPs** are responsible for the successive and multiple biochemical reactions happening in different cells all over the body



- ❖ The compounds generated during the reactions (ROS and LOPs) represent the “**ozone messengers**” and are responsible for the biological and therapeutic effects
- ❖ All of these compounds are potentially cytotoxic, luckily have a very short half-life (normally a fraction of a second)
- ❖ This concept emphasizes why the ozone dose must be precise and well calibrated against the antioxidant capacity of blood
- ❖ **ROSs** yield **EARLY** biological effects on blood, whereas **LOPs** trigger **LATE** effects.

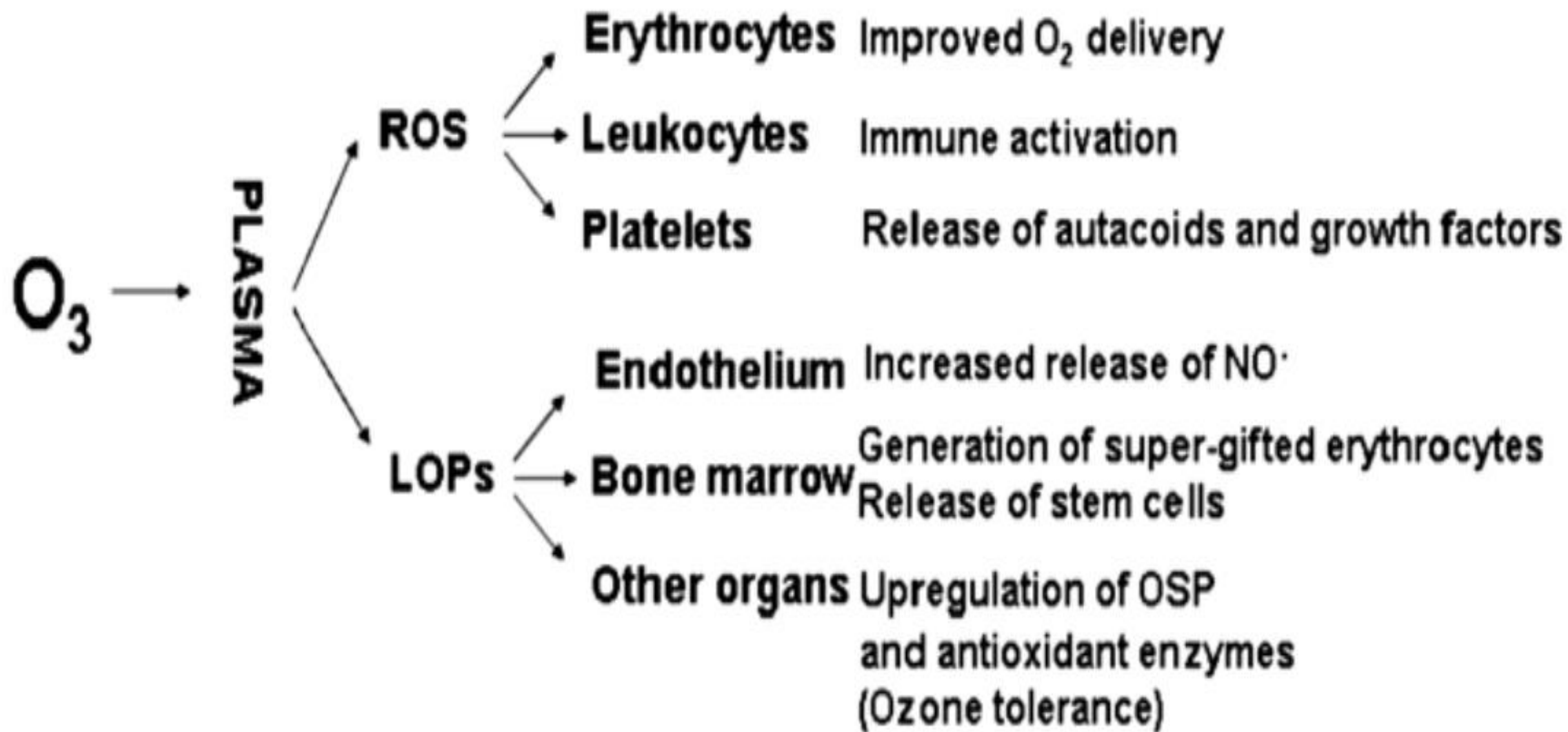


Substrates

Messengers

Targets

Functional modifications



Effect of ozone on the metabolism of oxygen

1. Changes in the rheological properties of the blood.
2. Increase in the speed of glycolysis of the erythrocyte.
 - ❖ Partial Oxygen Pressure (PO₂) in arterial blood and at the same time a decrease in the PO₂ in the venous blood.
 - ❖ The newly generated erythrocytes possess a G-6PD activity greater than that of the old ones, for which reason they have been referred to as "super-gifted erythrocytes".
3. The beneficial effect of this gas on another element, nitric oxide, has also been shown (maintaining optimal levels of vasodilation)

Modulator agent of the immune response

- Ozone therapy has an immune-modulating action, through the synthesis or release of immune-stimulating or immune-suppressing cytokines.
- The immunological actions of ozone on the blood is directed, fundamentally, to the monocytes and to the T lymphocytes
- This regulation is given because the ozone acts as an enhancer of the immunological system by activating the neutrophils and stimulating the synthesis of some cytokines.
- The optimization of the oxidant and antioxidant systems of the organism

Bactericide effect of ozone

- Ozone is capable of killing all the known types of gram-positive and gram-negative bacteria
- The local disinfectant, antiviral and antibacterial effects of ozone, therefore, are due to its germicide capacity, basically to its high oxidant capacity on the bacterial walls.
- Classic mechanisms of microbial resistance do not act with ozone.

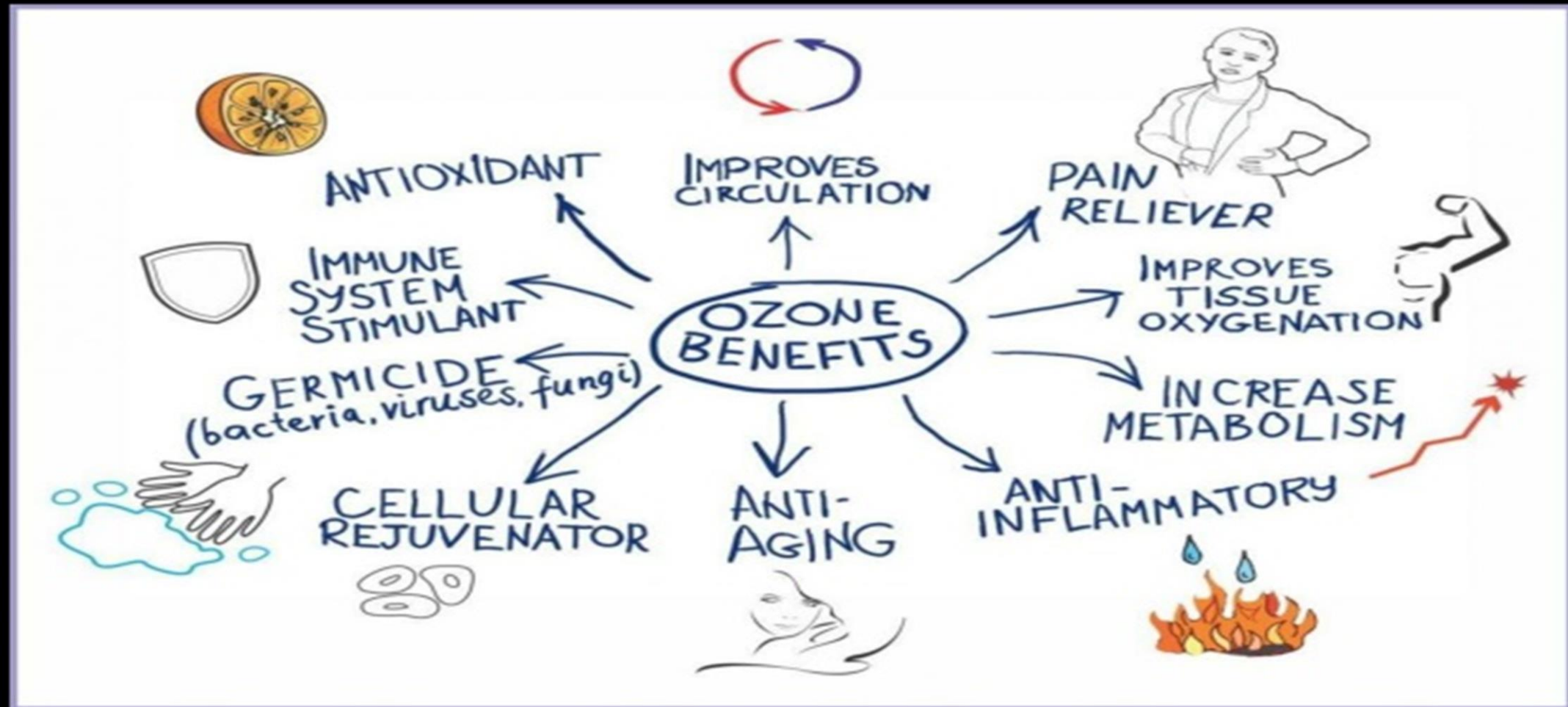
Action mechanism of ozone therapy on pain

- Ozone has a dual action mechanism: analgesic and anti-inflammatory.
- These effects seem to be due to its way of acting on diverse targets:
 - 1) Decrease the production of mediators of the inflammation.
 - 2) The oxidation (inactivation) of metabolic mediators of pain.
 - 3) It clearly improves local blood microcirculation
- Recent studies have elucidated the role of ROS in hyperalgesia by activating N-methyl-D-aspartate receptors

Anti-tumoral effect on tumor cell

- We can say that ozone therapy is "controlled oxidative stress" given to the body.
- Tumor cells have "anaerobic metabolism".
- When O₃ gas is used directly, it oxidizes the outer lipid layer of malignant cells and lysis.
- Since tumor cells have a primitive life form, they have not been able to develop antioxidant systems (AOS) mechanisms
- O₃ therapy can be used in conjunction with conventional treatments for cancer.

Benefits Of Ozone Therapy



How Is Ozone Administered?



- Many **parenteral** and **topical** routes are used to administer ozone without toxic effects and minimal discomfort

Parenteral	Topical or locoregional
Intravenous (IV)	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)	
(A) Periarticular	Rectal
(B) Myofascial	
Intradiscal (ID)	Cutaneous
Intraforaminal (IF)	Dental
Intralesional (IL) ^c	

❖ With Systemic Effects:

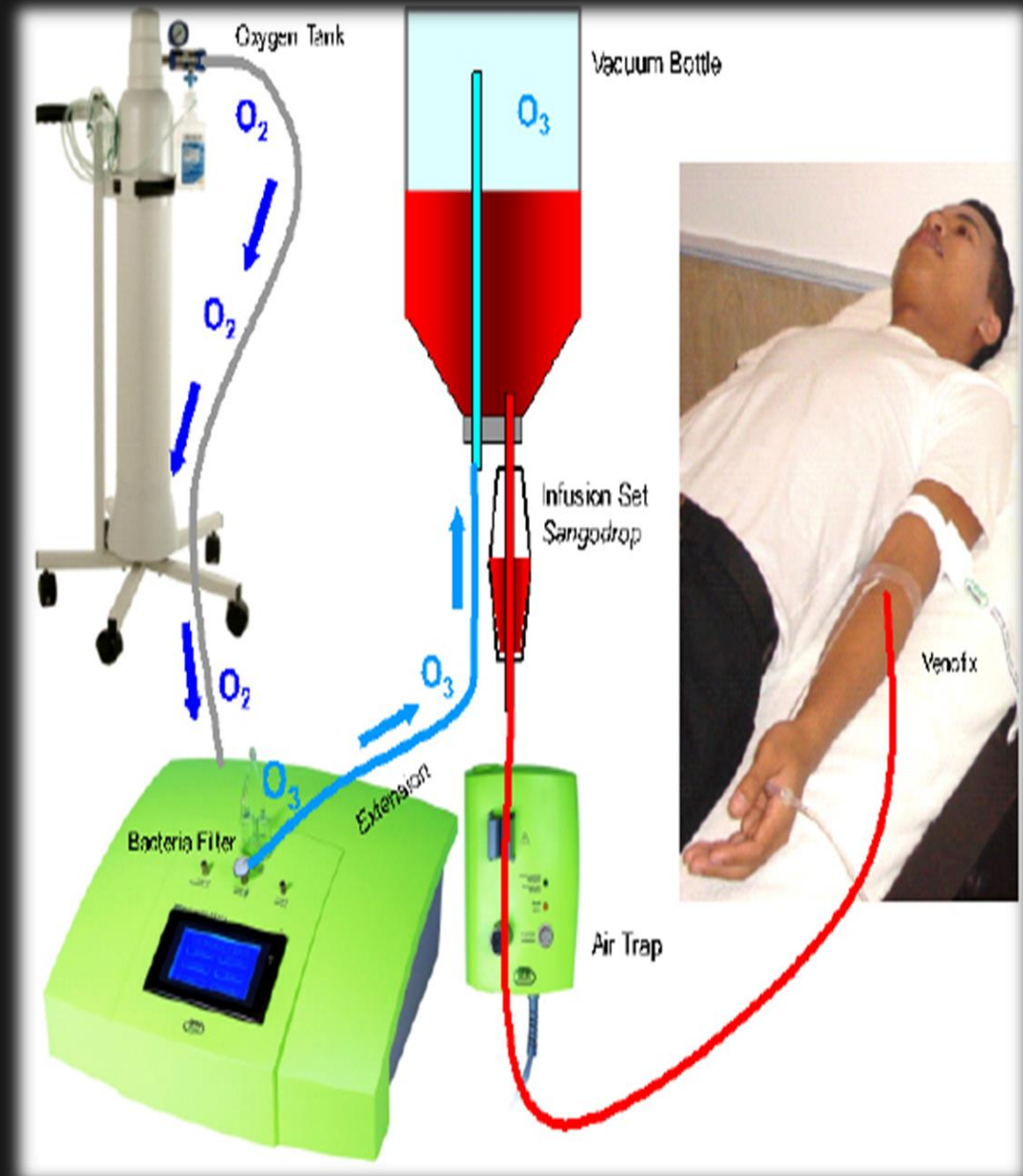
- Major Autohemotherapy
- Minor Autohemotherapy
- Extracorporeal blood oxygenation and ozonation (EBOO)
- Ozonated Saline

❖ With Local Effects:

- Rectal or vaginal ozone application
- Intra-articular and Intra-discal injection
- Injection into the muscles (Paravertebral)
- Ozonated water and Ozonated oil

Major Autohemotherapy

- Major Autohemotherapy (MAH) was originally developed by Dr. Hans Wolff, in Frankfurt, Germany, in the late 1960s.
- It is very safe, virtually free of negative side effects, and permits an ozone dosage range from very low to very high.
- It is recommended, either as only treatment or in combination with other forms of ozone therapy, or other medication



- MAH session should be done by a **physician, adequately trained in ozone therapy.**
- Autohemotherapy is the preferred method of many practitioners, and it is used in well over 150 diseases.
- In **Germany**, even the ambulances are equipped with **ozone generators**; if ozone is administered within 24 hours of a stroke, 95% of patients suffer no permanent paralysis



Indications

- ❖ Arterial circulatory disturbances
- ❖ Angiopathy
- ❖ Viral diseases
- ❖ General immune deficiency
- ❖ Chronic inflammatory processes in orthopedics and rheumatology
- ❖ Complementary concept in oncology
- ❖ Pre-conditioning for patients who plan to undergo major surgery

Contraindications

Absolute contraindication: Favism: G6PD deficiency

(this enzyme is necessary for supply hydrogen ions to the glutathione system)

❖ Relative contraindications :

- Uncompensated diabetes
- Pregnancy, especially in the first 3 months
- Uncompensated toxic hyperthyroidism
- Thrombocytopenia less than 50.000 and serious coagulation disorders
- Severe Cardiovascular instability
- Acute alcohol intoxication
- Acute infarction of myocardium
- Massive and acute hemorrhage
- During convulsive states
- Hemochromatosis
- Patients receiving treatment with copper or iron

- Test of G6PD is recommended prior to O₃ therapy in order to avoid complications.
- After myocardial infarction ozone therapy can be used not earlier than after 6 months of Infarct
- In patients with hemorrhagic insult ozone therapy is not recommended for use.

Minor Autohemotherapy (MiAH)

- Minor Autohemotherapy (MiAH) involves mixing the blood of the patient removed intravenously (5 mL-10 mL) without anticoagulant, drawn into a sterile, pyrogen-free disposable syringe (already containing the ozone-oxygen mixture, 10 $\mu\text{g}/\text{NmL}$ to 40 $\mu\text{g}/\text{NmL}$).
- The blood and ozone mixture is intensively shaken and slowly reinjected intramuscularly in the ventrogluteal region along with the gas.
- MiAH is an immune stimulant therapy, comparable to "Auto-vaccination"
- Cycles: of 5-10 treatments once a week.



Indications

- ❖ Its main indication is in all dermatological diseases. As an auto vaccine in psoriasis, dermatitis, eczema, acne vulgaris, allergies
- ❖ As an adjuvant in cancer or in chronic debilitating pathologies

Ozonized Saline Solution (O3SS)

- Ozonized Saline Solution (O3SS) is a widespread practice in Russia
- Some recent studies use this in Acute appendicitis, Brain trauma, Diabetic foot, Obstructive jaundice, Delayed fetal growth and Lymphovenous failure of lower limbs.
- The ozonized saline solution (O3SS) is carried out with very low ozone concentrations which are calculated according to the weight of the patient.
- Low ozone dose: 1 $\mu\text{g}/\text{kg}$.
Medium ozone dose: 2 $\mu\text{g}/\text{kg}$.
High ozone dose: 5 $\mu\text{g}/\text{kg}$

- Please note that the dissolved ozone concentration is 25% of the ozone gas concentration in the saline solution.
- This has to be taken into consideration when calculating the concentration set at the ozone generator: it has to be multiplied by 4 in order to get 100% of the dose needed
- $\text{Dose } (\mu\text{g}) = \text{dissolved ozone concentration } (\mu\text{g/mL}) \times \text{Volume (mL) saline solution.}$

Ozone sauna therapy

- It is the combination of sauna and ozone gas.
- During an ozone sauna you sit in a sauna box which induces sweating and into which ozone is introduced at the same time.
- It's important that the sauna allows for the head to stick out to prevent you from inhaling the ozone gas.
- A great way to detox as it increases the cleansing capacity of the skin via stimulation of the sweat glands.
- It also increases blood circulation in the body which promotes healthy skin.



BENEFITS OF OZONE SAUNA THERAPY

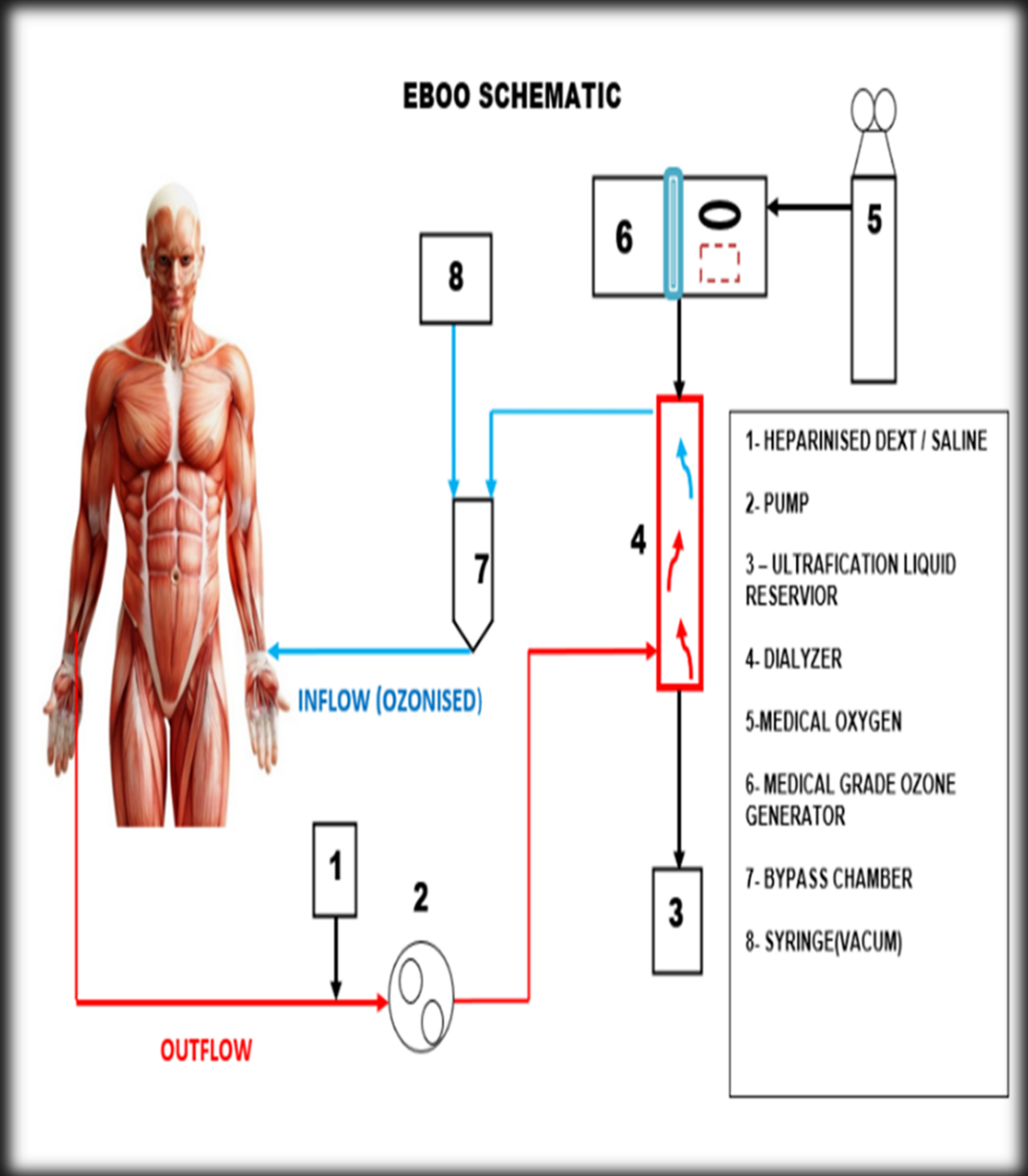
- Dramatically increase oxygenation of the tissues and cells
- Burn 400-600 calories per session
- Stimulate the Immune System and Increase the White Blood Cell count
- Increase circulation, oxygen and nutrient delivery within the body
- Increase 2,3-DPG and then the blood's ability to release oxygen in tissues
- Increase tumor necrosis factor by up to 500 times
- Purge the body of accumulated toxins

Extracorporeal Blood Oxygenation-Ozonation (EBOO)

- The method EBOO is an advanced variant of the MAH.
- The EBOO is similar to a hemodialysis, amplifies the therapeutic benefits reported of MAH by treating a greater volume of blood (4 L/h) at a lower ozone concentration (<1 µg/mL).
- This method is used in Italy, Russia, Ukraine, Malaysia, and rarely in some Latin American countries, mainly to treat severe peripheral arterial disease, coronary disease, severe dyslipidemia, necrotizing fasciitis, septicemia infection resistant to antibiotics, ischemic stroke, chronic heart failure and viral hepatitis C.

➤ The procedure EBOO represents a simultaneous oxygenation and ozonation of blood which is transferred from one vein system of the patient to a gas exchange device (GED), and then from GED into another venous system.

➤ Upper and lower veins can be used for this procedure.



Rectal Insufflation

- The Rectal insufflation of ozone is a **systemic route**.
- The gas is quickly dissolved in the luminal contents of the bowel, where mucoproteins and other secretory products with antioxidant activity readily react with ozone to produce ROSs and LPOs.
- These enter the circulation of venous and lymphatic capillaries.
- This non-invasive technique can be used without risk in pediatric and elderly patients, and on patients with difficult access of veins for MAH.
- It can be used in **metastatic cancers to liver**.

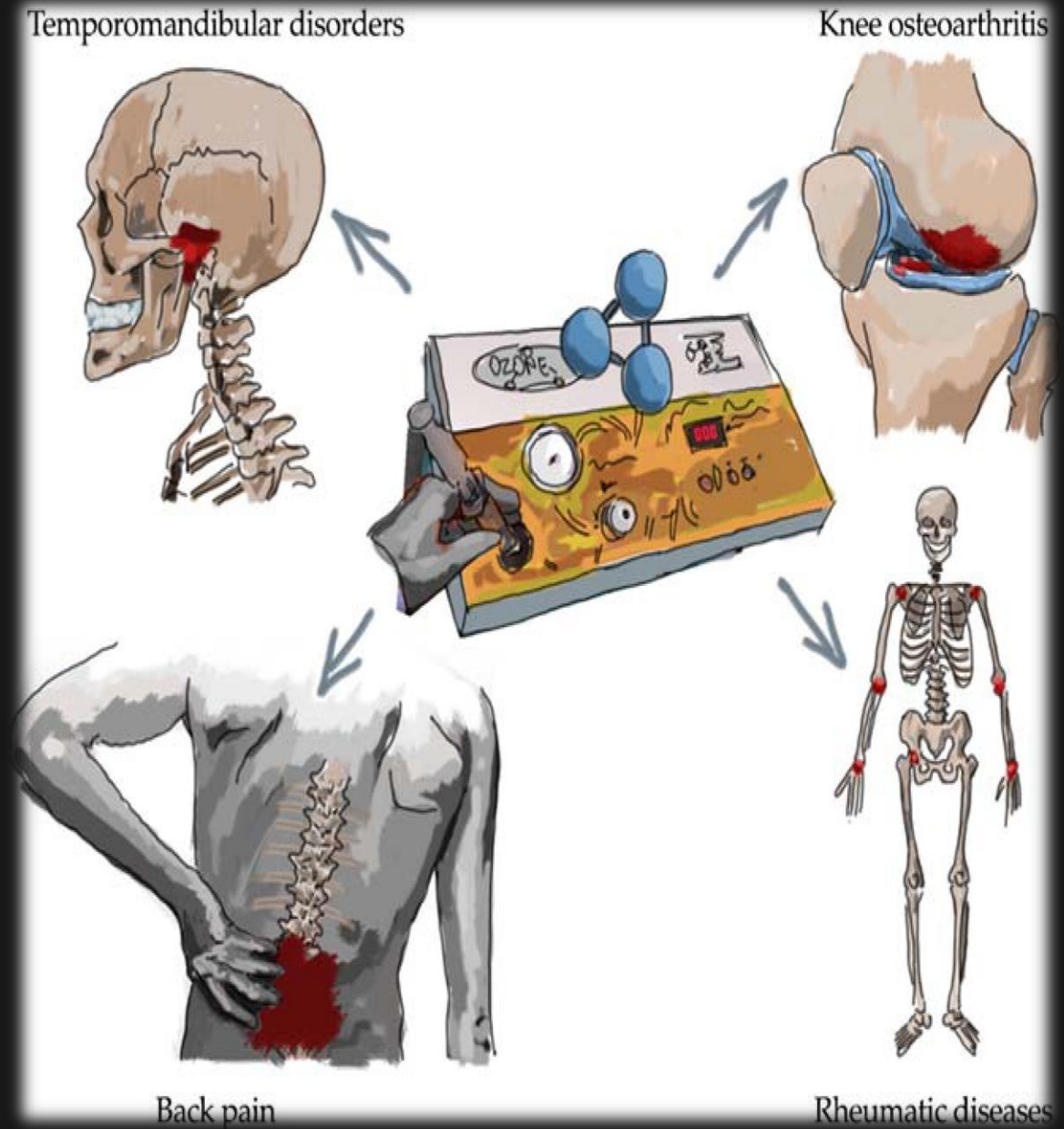


Ozone therapy

in

Pain Medicine

- Anti-inflammatory, analgesic, and anti-edema properties of injected medical ozone,
- The oxidation of the algogenic receptors would inhibit the pain signal and it would activate the antinociceptive system
- A muscle relaxant effect, as well as improved mobility of the treated area that can be observed clinically

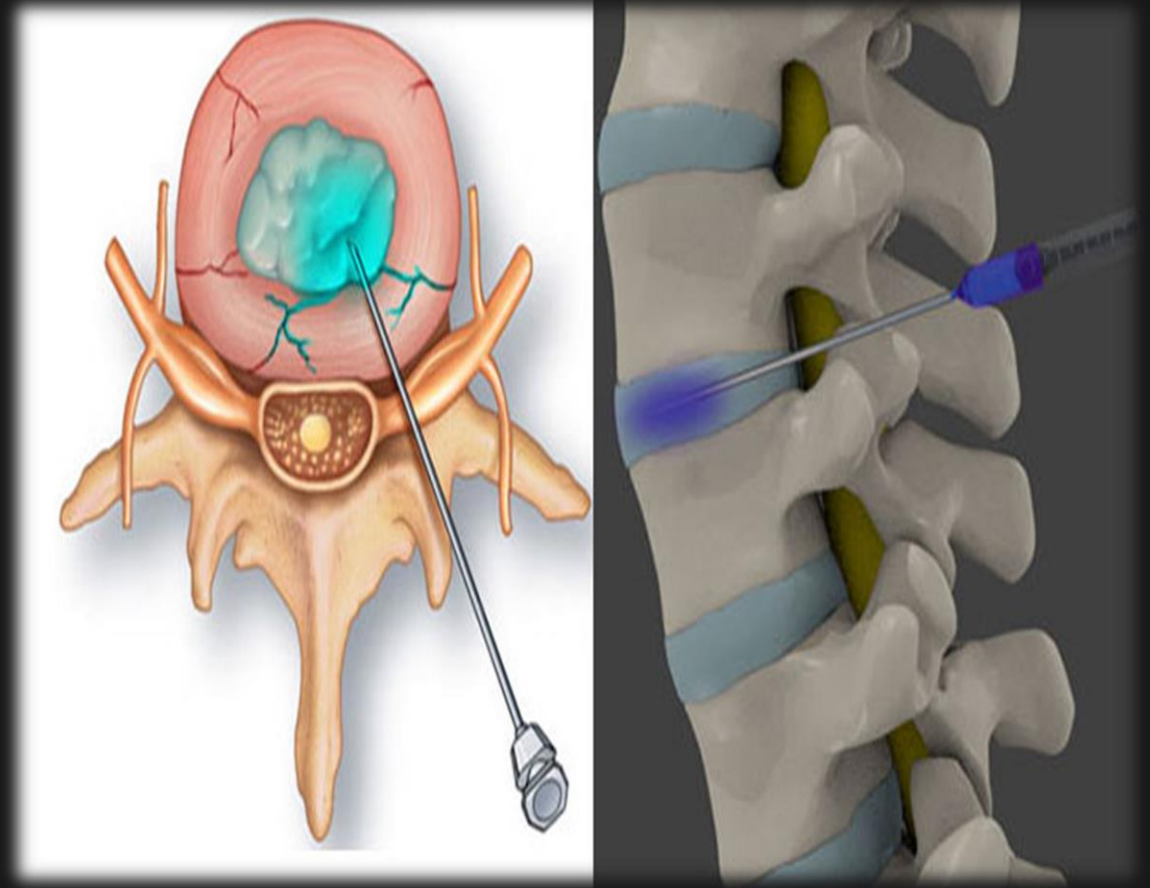


Intradiscal Ozone Injection

there is a dual ozone action mechanism in the Radicular Compression Syndrome:

- A. The dehydration of the material disc that would reduce the compressive mechanical factors on the root
- B. Interrupting the inflammatory process with immediate installation of an analgesic effect.

- ❖ The nucleus pulposus of the herniated disc contains very high values of phospholipase A2 which can initiate the inflammatory cascade
- ❖ The nucleus pulposus of the hernias contain a large part of water and mucopolysaccharides



- ❖ ROS will react with aminoacids and carbohydrates of proteoglycans and collagen I and II that make up the matrix
- ❖ The O₃ causes lysis or dispersion of the water and oxidation of the mucopolysaccharides
- ❖ The collapse releases the trapped water, which, after being reabsorbed, permits reducing the intradiscal pressure and the consequent disappearance of the pain, by decreasing the compression on the nerve root.

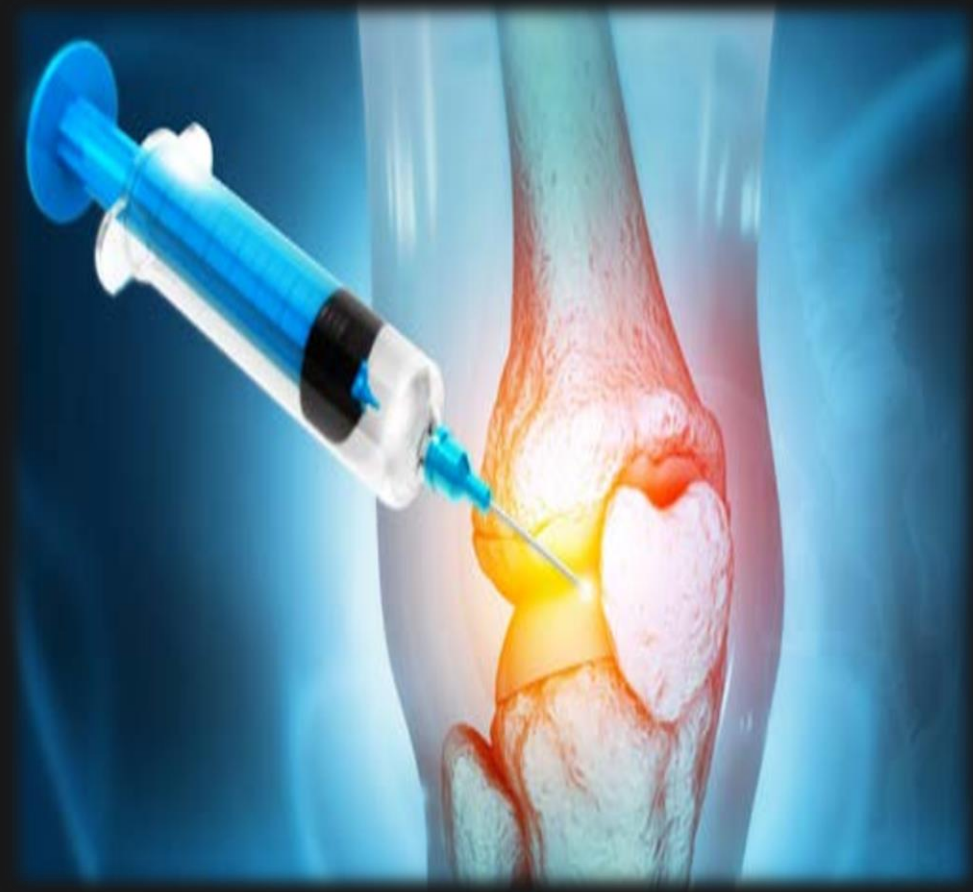
process of "mummification" which would shrink the disk, reducing the compression

Thus, intradiscal and paravertebral ozone works on different levels:

1. Inhibition of prostaglandin E2 and phospholipase A2 (similar to steroids) and other cytokines pro-inflammatory.
2. Increase in the release of immunosuppressive cytokines (IL10, factor B1): analgesic and anti-inflammatory.
3. Increase of local microcirculation, reduces venous stasis: analgesic effect, because the nerve root is very sensitive to hypoxia.
4. Presentation of a direct effect on the mucopolysaccharides and proteoglycans from the pulposus nucleus, which is called ozonolysis, (chemical discolysis with water loss and dehydration)
5. Subsequently, there is a matrix degeneration, which is replaced by collagen fibers in approximately five weeks, and by the formation of new blood cells: reducing the volume of the disc

Ozone Therapy in Knee Pathology

- ❖ The treatment consisted of intra-articular and periarticular infiltrations of 10 ml of medical ozone at a concentration of $20\mu\text{g/ml}$.
- ❖ Six systematic reviews and meta-analyses were published in different journals supporting the use of ozone in knee osteoarthritis with a high level of evidence
- ❖ Peritendinosus injected ozone has been used with success in refractory knee tendinopathies
- ❖ Patellofemoral chondromalacia is a painful pathology whose treatment is mainly surgical, and patients with injected O_2/O_3 are obtaining a higher and faster resolution of the pain after surgery.



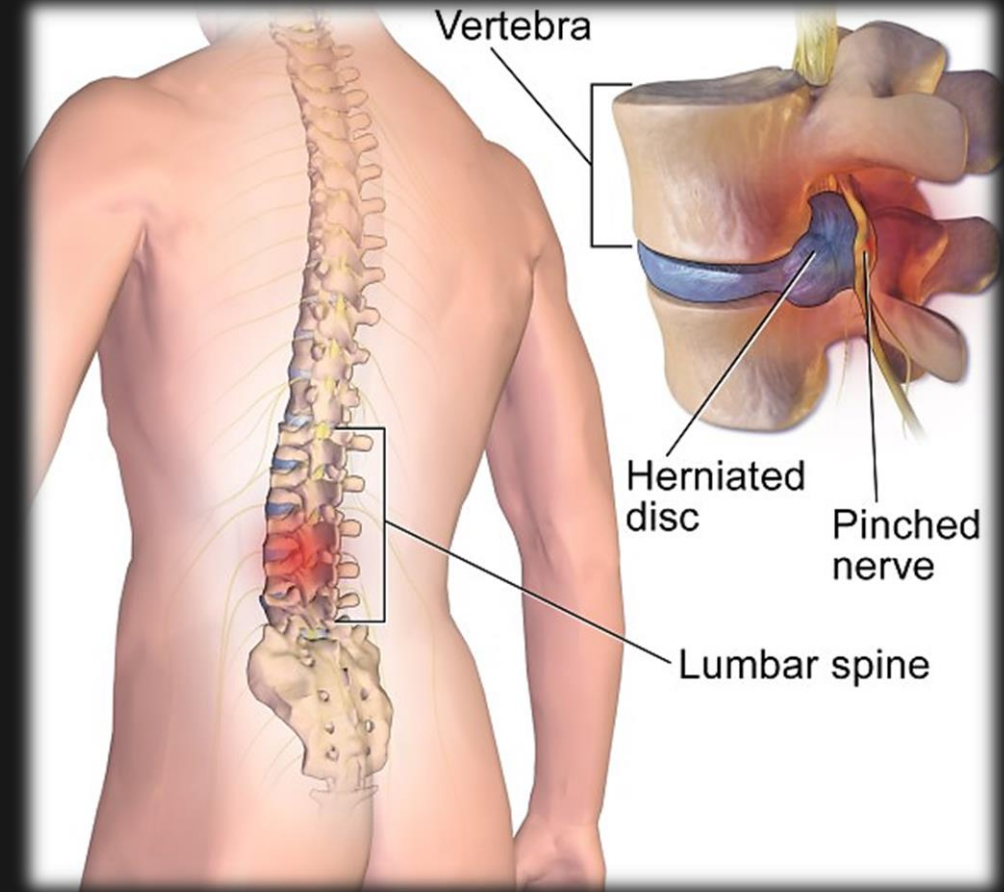
Ozone Therapy in Shoulder Pathology

- ❖ A prospective controlled study of patients suffering from subacromial tendinopathy treated with injected ozone showed superior clinical results.
- ❖ Oxygen-ozone therapy has also been used successfully to treat calcifying tendinitis of the shoulder
- ❖ Utility of ultrasound-guided O₂/ O₃ infiltrations in patients with non-surgical lesions of the rotator cuff.



Ozone Therapy in Spinal Pathology

- ❖ Ozone therapy for the treatment of herniated disks, both cervical and lumbar
- ❖ The treatment of cervical herniated disks is generally more conservative than that of the lumbar
- ❖ The analgesic, anti-inflammatory, and muscle relaxant effects of the ozone therapy in cervical pathology
- ❖ Comparing with other minimally invasive techniques, ozone therapy was an effective, safe, and minimally stressful technique
- ❖ In Failed back surgery syndrome (FBSS) more conservative and less invasive treatments, such as ozone therapy has effectiveness between 65 and 80%



Infiltrative Ozone Therapy in Rheumatoid Arthritis

- ❖ Some doctors use ozone therapy **empirically** in patients with rheumatic diseases using joint infiltrations for years, supposedly with very positive results, but there are no major works published in this regard.

Other Applications of Infiltrated Oxygen/Ozone

- Tendinopathies
- Neural entrapment syndromes
- Lateral epicondylitis
- Spondylolisthesis
- Spondylolysis
- Plantar fasciitis
- Septic spondylodiscitis
- D'Quervain's tenosynovitis
- Metatarsalgia due to postsurgical fibrosis after resection of Morton's neuroma
- Temporomandibular joint pathology

SYSTEMIC OZONE THERAPY IN PAIN MEDICINE

- Systemic ozone therapy would help patients with **chronic pain**, as recent preclinical studies have demonstrated the role of ROS in hyperalgesia, via activation of the **N-methyl-D-aspartate (NMDA) receptors**.
- In both **neuropathic and inflammatory pain**, ROS is increased at the dorsal horn and that systemic administration of a neutralizing agent of ROS reduce the hyperalgesia by blocking phosphorylation from NMDAs.
- **Fibromyalgia** seems to be a "**stress disease**" and systemic ozone therapy shows very good tolerability and improvement in pain and fatigue, as well as a significant decrease in the use of pain medication.

OZONE THERAPY SIDE EFFECTS

- Vary depending on the type of treatment a person undergoes.
- People should **never inhale ozone**.
- If it enters the mouth, nose, or eyes, it can **burn** and cause **coughing, nausea, vomiting, or headaches**. More severe exposure can lead to **respiratory complications**.
- People who undergo ozone therapy sometimes experience the **Herxheimer reaction (flu-like symptoms)**
- If someone receives ozone therapy via the **rectum**, they may experience **discomfort, cramping, and a feeling of needing to pass gas**. These side effects are temporary.

- The incidence of effects adverse effects of systemic ozone therapy was only 0.0007%, mainly nausea, headache, and fatigue.
- The most serious common adverse effect would be a vagal reaction, generally associated with pain during infiltration.
- Injection must be done slowly, especially if a large gas volume at a high concentration is used



Thank
You
For
Your
Attention