Ozone in Medicine: Overview and Future Directions

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Abstract:

Ozone, an allotropic form of oxygen possesses unique properties which are being defined and applied to biological systems as well as to clinical practice. As a molecule containing a large excess of energy, ozone, through incompletely understood mechanisms, manifests bactericidal, virucidal and fungicidal actions which may make it a treatment of choice in certain conditions and an adjunctive treatment in others.

Introduction

Ozone, best known for its protective role in the earth's ecological harmony, and for its interaction at ground level with industrial pollutants, has unique biological properties which are being investigated for applications in various medical fields.

As early as the First World War, ozone's bactericidal properties were used to treat infected wounds, mustard gas burns and fistulas. These first treatment attempts, however, were hampered by technological difficulties. Medical ozone generators have since been developed and refined. They differ from industrial generators in their capacity to deliver the purest ozone-oxygen mixtures in precise dosages. A critical advance in medical ozone technology was the development, in the early 60's, of plastics which can adequately conduit this mixture and permit proper interfacing with patients. In the last few years ozone treatment has seen growing interest from diverse medical disciplines, and research is in progress to delineate its effects on biological systems and to define its clinical applications.

Historical Perspectives

The history of ozone's discovery is intrinsically entwined in the evolution of the earliest concepts in chemistry. Priestly and Cavendish noted that electrical sparks fired in a closed volume of air resulted in volume compression.[1,2] In 1785, Martinus Van Marum, subjecting oxygen to electrical discharges, noted "the odor of electrical matter" and the accelerated oxidation of mercury. In 1840, Schonbein repeated these experiments, concluded that this odor was due to a gas which he named ozone, from the Greek ozein (odorant), and described several of its properties.[3] Numerous researchers since that time have worked to elucidate the nature and actions of ozone. Still today, theoretical issues

remain regarding its electron structure, the varieties of its molecular configurations and its kinetics. Mariniak and Delarive showed that it is an allotropic form of oxygen, and Mulliken and Dewar clarified its molecular architecture.[4]

In the latter part of the 19th century, ozone was found to oxidize a spectrum of organic compounds and to interact with double bonds. Chemists made use of these properties to study complex molecules by cleaving them into smaller fragments. Harries, by such methods, discovered the structure of natural rubber.[4]

The ability of ozone to destroy toxic or noxious industrial impurities (phenols, cyanides, tetraethyl lead among others) and to inactivate bacterial contaminants in sewage has made it an attractive alternative to chlorination. Wiesbaden, Germany became the first city to use ozonation for purification of its drinking water (1901), followed by Zurich, Florence, Brussels, Marseille, Singapore and Moscow (the largest installation in the world), among others. The history of ozone's medical applications has nebulous and anecdotal beginnings. Kleinmann is said to have carried out the first bacteriological studies on pathogenic organisms using the Siemens tube, shortly after its invention.[5] Payr,[6] and Fisch and Wolff[7] were clinician pioneers, and J. Hansler developed one of the first reliable models of medical ozone generators.[5,8]

Physico-Chemical and Biochemical Properties

The oxygen atom exists in nature in several forms: (1) as a free atomic particle (O), it is highly reactive and unstable; (2) oxygen (O2) its most common and stable form, is colorless as a gas and pale blue as a liquid; (3) ozone (O3), has a molecular weight of 48, a density one and a half times that of oxygen and contains a large excess of energy in its molecule (P3--) 3/2 O2 + 143 KJ/mole. It has a bond angle of 127 [3], which resonates among several forms, is distinctly blue as a gas and dark blue as a solid; (4) O4 is a very unstable, rare, nonmagnetic pale blue gas which readily breaks down into two molecules of oxygen.

Ozone is a powerful oxidant, surpassed in this regard only by fluorine. Shonbein,3 in 1855, discovered that it reacts with ethelene. Exposing ozone to organic molecules containing double or triple bonds yields many complex and as yet incompletely configurated ephemeral transitional compounds (zwitterions, molozonides, cyclic ozonides), which may be hydrolyzed, oxidized, reduced or thermally decomposed to a variety of substances, chiefly aldehydes, ketones, acids or alcohols. Ozone reacts with saturated hydrocarbons, amines, sulfhydryl groups and aromatic compounds.

Of importance to biological systems is ozone's interaction with tissue (especially blood) constituents. The most studied is lipid peroxidation although interactions have yet to be more fully investigated with complex carbohydrates, protein, glycoproteins and sphingolipids. These dynamics are especially relevant for medical applications because some of the most practiced methods in ozone therapy involve the mixing of a small volume of whole blood with a pure oxygen ozone mixture and subsequently returning it to the patient. In this manner, it is calculated that the dose of ozone administered will perform its therapeutic functions without disrupting blood constituents.

Since there are a variety of lipid components in whole blood, it is of more than theoretical interest to determine the end products of ozone per oxidation and their effects, not only on physiological systems but on

the integrity of ambient patholgenic organisms, since one of the mechanisms of viral inactivation is thought to be through this modality. Cholesterol accounts for 120 to 220 mg/100 ml, of which 60% to 75% are cholesterol esters; phospholipids 9 to 16 mg/100 ml; triglycerides 40 to 150 mg/100 ml, and free fatty acids 6 to 16 mg/100 ml. Given a total lipid concentration of 450 to 1000 mg/100 ml and the large variety of lipid constituents, the possible end products of ozonation are bountiful.[9,10]

This question is further complicated by the presence of systems to buffer lipid peroxidation, including vitamin E, uric acid,[11] and enzymes such as superoxide dismutase, catalase, and the glutathione peroxidase system which has gathered the most experimental attention.[12]

Several agents derived from lipid peroxidation include free radical, singlet oxygen, hydrogen peroxide, hydroperoxide, ozonides, carbonyls, alkanes and alkenes. Of these, lipid hydroperoxides, the most extensively studied, are known in sufficient concentrations to manifest their toxicity by altering cell membranes. Acted upon by glutathione peroxidase, they are reduced to their corresponding alcohols.

Method of Manufacture and Precautions

The production of ozone-oxygen mixtures for human and veterinary applications is subject to important technical consideration and standards. Clinical ozone generators which regulate the flow of medical grade oxygen through high voltage tubes with outputs ranging from 4000 V to 14000 V are capable of producing precise ozone-oxygen mixtures within concentration ranges extending to 5%, predicated on three variables: (1) the voltage applied; (2) the oxygen flow rate; and (3) the electrode separation distance. The purity of the oxygen source is especially emphasized since nitrogen, in the presence of high energy fields, forms toxic nitric oxides.

Since the half life of ozone is 45 minutes at 20C (68F), losing its concentration to 16% of its initial value in two hours, it must be freshly generated for immediate use at the treatment site. The maximum dose generated, 5% ozone to 95% oxygen, is well below the explosive limit (15 to 20%). Caution is needed not to appose ether and an ozone, an especially reactive mixture.

Listed contraindications to ozone treatment[5] include acute alcohol intoxication, recent myocardial infarction, hemorrhage from any organ, pregnancy, hyperthyroidism, thrombocytopenia and ozone allergy.

Methods of Administration, Dosage, and Clinical Applications External Ozone Gas Application

Historically, ozone was first administered by application to external body surfaces to determine its effects on a variety of lesions, A. Wolff,[13] in 1915, is credited for using local ozone treatments for wounds, fistulas, decubitus ulcers and osteomyelitis. Like natural rubber which cracks and fritters when exposed to oxygen-ozone mixtures, early materials caused ozone to "bag" around skin surfaces and met with early oxidation disuse. Today, specially designed plastics (Teflon) enable extremities or portions of the head or torso to be comfortably encased in a space where a determined dosage ratio of oxygen to ozone is administered at a chosen flow rate. In this way, the walls of the transparent bags do not touch the patient, an important consideration in burn treatment.

Indication for external ozone application include poorly healing wounds, burns,[14] staphylococcal infections, fungal and radiation lesions, herpes simplex and zoster, and gangrene (diabetic or Clostridium). Dosage is adjusted to the condition treated. Gas perfusions may last from 3 to 20 minutes, ozone concentrations varying from 10 to 80 ug/ml (maximum five parts of ozone to 95 parts of oxygen). High ozone concentrations are used for disinfection and cleaning (or debridement), while low concentrations promote epithelialization and healing.[6,15]

Ozone Insufflation

Payr in 1935[6] and Aubourg in 1936[16] first used ozone-oxygen mixtures in rectal insufflation to treat ulcerative colitis and fistulae. The list of indications has expanded to include proctitis and hemorrhoids. It is reported that in inflammatory diseases of the bowel, ozone promotes healing and restores the flora balance disturbed by pathogenic organisms. In a typical treatment for ulcerative colitis, daily insufflations are applied starting with 50 ml in severe cases, increasing as tolerated in increments (till 500 ml), high concentrations administered initially (75 ug/ml) to achieve hemostasis, followed by low concentrations to promote resolution.[5] This technique may have some promise in the treatment of bowel infections associated with AIDS.

Microsporidia, a tiny, rarely detected parasite may be responsible for many cases of AIDS wasting illness,[17] and studies await determination of its susceptibility to ozone treatment.

Major Autohemotherapy (AHT)

Whereas it can be readily understood that external ozone applications produce local effects such as disinfection, wound healing or local circulatory enhancement, the technique of introducing ozone into the circulation poses more complex theoretical issues. In the technique of major autohemotherapy, 50 to 100 ml of blood is drawn from the patient, mixed with a dose of ozone-oxygen of a predetermined concentration, then returned via the same intravenous catheter (butterfly). Returned to the patient, the ozonated blood is rapidly distributed to all tissues.

In the treatment aliquot of blood, it is gauged that the dose of ozone given not only will exert therapeutic actions locally (virucidal activity, oxygenation, increased red cell fluidity), but will determine beneficial systemic actions.[18]

The duration of time that ozone remains in solution and its effects on endocrine, neurological, and immunological systems are not known. Clinically, some patients, upon receiving their own ozonated blood, report a faint background taste of ozone, which may be an indication of its survivability in solution for at least a few seconds.

Major autohemotherapy has been applied to the treatment of several conditions, including acute and chronic viral infections (hepatitis), some carcinomas, circulatory disturbances (diabetes, arteriosclerosis), and hyperlipidemia.[8,19-21] Added to a standard pharmacotherapeutic regimen for postmenopausal osteoporosis, this technique enhanced remineralization of bone.[22] Clinical reports however, need to be substantiated by properly designed studies. Of interest are the reports of some patients, who after receivng this treatment experience feelings of well-being lasting for a few minutes to several hours. Whether this represents a placebo effect, a metabolic alteration or possibly a neuro-psychiatric mechanism remains to be determined.

Miscellaneous Applications

Although the above techniques of ozone administration represent the majority of hospital or office-based procedures, others deserve mention.

Minor Autohemotherapy

In this technique, 10 ml of venous blood is drawn from the patient, mixed with ozone-oxygen, then injected intramuscularly. Listed indications include asthma, acne, some allergic conditions and some carcinomas.[18,23,24]

Direct Intra-arterial or Intravenous Administration

Mostly of historical interest, this method was first used by Iacoste in 1951[25] for circulatory compromise

and its possible sequelae (gangrene). Up to 10 ml of pure ozone-oxygen may be slowly injected directly into the artery (usually femoral), or into a vein, without incurring embolization since both gases are readily soluble in blood.[20] Indications include intermittent claudication, leg ulcers and cerebral vascular insufficiency. Due to accidents produced by too rapid introduction of the gas mixture into the circulation, this technique is now rarely used.

Intramuscular Injection

Up to 10 ml of pure ozone-oxygen mixture is injected into the gluteus maximus muscle or the deltoid. This treatment along with major autohemotherapy is invoked as an adjunct to cancer therapy.[15,18,26,27]

Ozonated Water

Ozone is approximately 10 times more soluble in water than oxygen. Mixed into aqua bidestillata (pyrogen free) water, the half life of ozone is nine to ten hours (at pH 7 and 20C); and at 0C, it is doubled. Ozonated water finds applications in dental surgery where it is reported to promote hemostasis, enhance local oxygen supply and inhibit bacterial proliferation. Applied following tooth extraction or during dental surgery,[28] it may also be rinsed in conditions such as thrush and periodontal disease, swallowed in cases of gastritis or gastric carcinoma, or irrigated in chronic intestinal or bladder inflammation.

Ozone Ointments

Ozonated olive oil provides long term, low dose exposure of ozone and lipid peroxides to tissues. Decubitus ulcers and mycoses are indications for its use.[29,30]

Balneotherapy

Ozonated water bubbled in warm baths, provides stimulation of local circulation and disinfectant action to varicosities, peripheral circulatory disorders and dermatological conditions (eczema, ulcers).[5]

Blood Purification

The possibility of using ozone to sterilize blood supplies has been investigated by several authors.[7,31] The treatment of 500 ml of whole blood with 100ml of O3/O2 mixture (40 to 50 ug/ml) is reported to render it virus-free without injuring any cellular elements. One study [31] examined 10,000 samples and found no cases of hepatitis transmission. This technique may extend its efficacy to the HIV virus as one preliminary unpublished study indicates although once ensconced in the genetic cellular material, it is unclear how any agent could inactivate it without compromising cellular integrity.

Metabolic and Physiological Effects of Ozone

Most research on ozone's biological effects have concentrated on pulmonary responses with emphasis on its toxicity. Interest has been keen on ozone's role in ground level atmospheric pollution. Produced as a result of interactions between industrial gases, oxygen and ultraviolet rays, there is evidence of synergistic action on pulmonary compromise. The effects of pure ozone, however, need to be differentiated from those of smog.

The majority of studies have been performed on animals who show great interspecies variability in their response to inhaled ozone. Extrapolation to humans is difficult due to differences in pulmonary anatomy and physiology. Mice[32] seem to be the most sensitive (LD50, 22 ppm for 3 hrs) and birds[33] the least (turkeys survived 417 ppm ozone for 3 hrs). While overdose is marked by pulmonary edema and hemorrhage, long term, low level exposure produces poorly understood, sometimes contradictory findings.

Reported effects[34] include enhanced enzyme activity, as evidenced by increase in glucose utilization,

lactate and CO2 formation and elevated glucose-6-phosphate dehydrogenase; an increase in the NADPH-cytochrome P-450 content in rat lung pointing to enhancement of metabolizing enzymes; increased lung fibroblast glucose uptake, and production of lactate and pyruvate.

Humans exposed to ambient ozone (0.24 ppm in room air for two hours) typically develop mild accelerated breathing in the context of symptoms such as tracheal or laryngeal irritation and chest tightness on inspiration. Large intersubject response differences are notable.[35] Athletes[36] performing moderate intermittent exercise show a 7% drop in Forced Vital Capacity (FVC) and a 15% reduction in Forced Expiratory Volume (FEV). The threshold for significant changes in respiratory compromise ranges from 0.15 ppm[37] to 0.25 ppm,[38] increasing ozone concentrations yield corresponding airway hyper-responsiveness through bronchoconstriction. Histological findings extrapolated from primate research points to ciliated cell inhibition and type 2 cell proliferation, increased membrane permeability and variable inflammatory response.[12] Reported biochemical alterations[39] include increased oxygen consumption and glucose utilization; activation of NADPH, superoxide dismutase, GSH peroxidase, GSH reductase and glutathione peroxidase. Pulmonary effects from ozone in low doses appear to include metabolic activation of lung cells while higher doses produce evidence of cellular metabolic compromise.

In the methodology of ozone treatment, care is given to avoid the escape of ozone into the treatment area and modern machines are equipped to catalytically convert excess ozone to oxygen during administration. Interestingly some studies point to possible beneficial effects of low dose ambient ozone.[40,41] The phenomenon of ozone tolerance or adaptation the response to ozone exposure decreasing with time and finally evolving to a plateau occurs in both humans and animals.[38] Its significance remains obscure.

For the reason that below 0.30 ppm the probability of ozone traversing the respiratory epithelium and entering the systemic circulation is so low, very few studies have attempted to measure these effects.[39] In the technique of major autohemotherapy and others that involve the direct introduction of ozone into the circulation, however, this question is of special relevance. Studies of human blood in young adult males exposed to 0.50 ppm ozone for 2-3/4 hours[42] show significant changes in erythrocytes (RBC) as well as in the serum. RBC membrane fragility, glucose-6-phosphate dehydrogenase and lactate dehydrogenase enzyme activities were increased, while RBC acetyl cholinesterase and reduced glutathione reductase were not significantly changed. Serum vitamin E and lipid peroxidation levels were significantly increased. These findings indicate that ozone exposure increases metabolic activation parameters in red blood cells.

According to other researchers,[20,24,43] the direct intravascular injection of pure oxygen-ozone mixtures results in the following responses: (1) an activation of enzymes involved in peroxide or erythrocytes, an outgrowth of which is (2) stimulation of the [2,3] Bisphosphoglycerate cycle, shifting the oxyhemoglobin dissociation curve to the right thus releasing oxygen to the tissues. Further physiological effects include (3) an enhanced oxidative decarboxylation of pyruvate with the formation of Acetyl-CoA, and consequent citric acid cycle activation, (4) a direct influence on the mitochondrial transport system with reduction of NADH and oxidation of cytochromes, and (5) an increase in RBC pliability, blood fluidity, and arterial PO2.

Mechanisms of Bactericidal, Virucidal and Fungicidal Action

Although the inhibitory and lethal effects of ozone on pathogenic organisms have been observed since the latter part of the 19th century, the mechanisms for these actions have not yet been satisfactorily elucidated. Ozone is a strong germicide needing only a few micrograms per liter for measurable action. At a concentration of 1 g/m3 H2O at 1C, ozone rapidly inactivates coliform bacteria, staphylococcus aureus and Aeromonas hydrophilia.[44]

The inactivation rate of enteroviruses[45] is more rapid than for E. coli, takes place in relatively small concentrations of ozone, and is influenced by pH, temperature, and the presence of ambient organic compounds.

Viruses differ in their susceptibility to destruction by ozone. The resistance of polio virus type 2 was 40 times that of coxsackie AS,[46,47] and in an experiment using a continuous flow mixed reactor under controlled laboratory conditions, relative resistance in descending order was found to be: polio virus type 2, echovirus type 1, polio virus type 1, coxsackie virus type B5, echovirus type 5, coxsackie virus type A9. In pure water, at maximal solubility of ozone and room temperature, Echovirus type 29 is inactivated in one minute, polio virus type 1 in two, type 3 in three and type 2 in seven minutes.

The cell envelope of Gram negative microorganisms such as E. coli is a complex multilayer system composed of an inner cytoplasmic membrane made of phospholipids and proteins invaginating into the cytoplasm, a peptidoglycan layer, and an outer membrane of poly polymers such as polysaccharides. Gram positive cells have a less complex, three layer envelope with a thick peptidoglycan middle layer.

The most cited explanation for ozone's bactericidal effects centers on disruption of envelope integrity through peroxidation of phospholipids and lipoproteins. There is evidence for interaction with proteins as well.[48] In one study[49] exploring the effect of ozone on E. coli, evidence was found for ozone's penetration of the cell membrane, reacting with cytoplasmic substances and converting the closed circular plasmid DNA to open circular DNA, which would presumably lessen the efficiency of bacterial proliferation. It is notable that higher organisms have enzymatic mechanisms to restabilize disrupted DNA and RNA, which could provide a partial explanation for why, in clinical treatment with ozone at doses prescribed, ozone appears to be toxic to infecting organisms and not to the patient.[50]

Ozone possesses fungicidal effects, through poorly understood mechanisms. In one study, Candida utilis cell growth inhibition with ozone was greatly dependent on phases of their growth, budding cells exhibiting the most sensitivity to its presence.[51] Interestingly, in another study,[52] low doses of ozone stimulated the growth and development of Monilia fructagen and Phytophtora infestans, while higher doses were inhibitory.

Viruses are parasites at the genetic level, separated into families based on their structure, type of nucleic genome and mode of replication. Many virions contain a phospholipid envelope with glycoprotein spikes, encasing the nucleocapsid which contains nucleic acids (DNA or RNA), and structural proteins (including enzymes).

Lipid-containing viruses are sensitive to treatment with ether, assorted organic solvents, and ozone, indicating that disruption or loss of lipids results in impaired or destroyed infectivity. Viruses containing lipid envelopes include the Herpes viridae a large family grouping the Simplex, Varicella-Zoster, Cytomegalovirus and Epstein-Barr viruses; the Paramyxoviridae (mumps, measles); the Orthonyxoviridae (influenza); the Rhabdoviridae (rabies); and the Retroviridae (HIV). The HIV virus has an outer envelope made of a double layer of lipids penetrated by proteins of several types encasing two molecules of RNA.[53]

Many of the above viruses have complex, sometimes baffling life cycles and replicative strategies with progressions from host cell attachment of the virus particle, to penetration, uncoating of the viral envelope, synthesis of molecular components, and release of new generations of virions to the surrounding medium, most often through cell lysis. Many chronic viruses have eclipse phases alternating with phases of viremia, when waves of viral particles flood the bloodstream.

In view of the above considerations, what part can ozone play as an antiviral agent? In one study,[46] polio virus 1 was exposed to 0.21 mg/liter of ozone at pH 7.2. After 30 seconds 99% of the viruses were inactivated (lost their ability to replicate within host cells), but appeared to maintain their structural integrity. Analysis of viral components showed damage to polypeptide chains and envelope proteins, which could result in attachment capability compromise, and breakage of the single-stranded RNA into two parts, producing replicating dysfunction at its root level. Other researchers[54] in similar experiments concluded that in ozonation, it is the viral capsid which sustains damage. It is to be noted however, that the polioviridae (Picornavirus family) contain four structural proteins encapsulating a single RNA strand and are devoid of

lipids.

In those clinical applications which make use of external (or body cavity) application of ozone, it can be appreciated that in view of the fact that a direct ozone-organism contact exists, inactivation of micro-organisms, bacteria, viruses or fungi, proceeds by any one of a variety of different mechanisms. The treatment of burns, superficial mycotic infection, decubitus ulcers and abscesses is applied by this method. Theoretical issues present themselves, however, when examining treatment strategies aimed at systemic infections, notably viral afflictions which make use of introducing ozone-oxygen mixtures into the bloodstream (usually major AHT). The ozone-treated aliquot of blood which is reported to be rendered viral-free through direct contact with ozone and ozone peroxides,[5] is reintroduced into the circulation. Since very little free ozone remains in solution due to its high reactivity, it is its products mainly lipid compounds, possibly others which are thought to interact with circulating as well as tissue-bound virions, thus inactivating them.

Within the dose ranges prescribed (up to 10 mg (O3/100 ml of blood), we may be curious to measure this overflow antiviral capacity. Although unproven to be outright curative for any viral illness, ozone blood treatment, as reported in several studies[21,31,55] may lessen clinical severity or duration. Thus therapeutic benefits have been noted in hepatitis, acute and chronic, and herpes.[55] In chronic viral infections Cytomegalic, Epstein-Barr and Retroviridae (AIDS) among others blood ozonation performed in viremic cycles or in periods of clinical exacerbation may, through direct action, through the production of cofactors inhibitory to viral replication, or through modification of immune function, be used in inducing viral quiescence. Ozone is reported to be an immuno-stimulant in low doses and immuno-inhibitory at higher levels.[15,26,27]

It is not inconceivable, in view of the possibilities given to ozone's antiviral properties that new generations of machines may be developed to test the therapeutic potential of the extra-corporeal treatment of circulating blood.

Ozone Treatment in Cancer

The logic sustaining the use of oxygen-ozone application to the treatment of carcinomas rests on the strategy of capitalizing on the disturbed metabolism of cancer cells. Since the first bio-chemical hypothesis of cancer was proposed by Warburg[56] in 1925; that all tumors have higher rates of glycolysis under aerobic conditions than do nontumor cells, efforts have been made to find the variations which could best affect treatment strategy. Although his statement has subsequently been amended considerably, there is a massive and evolving body of research centering on biochemical differences between normal and malignant cells.[57]

Some tumors have high rates of glucose use and lactic acid production in the presence of oxygen, a reflection of a number of possible mechanisms, from membrane transport differences to variations in ATP regulation. Cancer cell mitochondrial ribosomes have altered J structure and function which could diminish their oxidative energy producing abilities thus accounting for their limited aerobic potential.[57]

Some authors[5,26] report a peroxide intolerance in tumor cells. Possessing insufficient catalase and peroxidase, they are incapable of effective peroxide inactivation. Such cells exposed to ozone are said to show a significant decrease in lactate content, indicating that ozone may induce metabolic inhibition in some carcinomas.

In one study,[58] cultured cells of different carcinoma types were compared with non-cancerous human lung fibroblasts on exposure to ozonated air (0.3, 0.5, and 0.8 ppm of O3 for 8 days). Alveolar (lung) adenocarcinoma, breast adenocarcinoma, uterine carcinosarcoma and endometrial carcinoma showed 40% cell growth inhibition at 0.3 ppm and 60% at 0.5 ppm. The non-cancerous lung cells were unaffected at these levels. In 0.8 ppm exposure, cancer cell growth inhibition was 90%. Interestingly, it was at this level that the

control cell group started to manifest anabolic slowdown (50%). The authors postulate that cancer cells are less able to compensate for the oxidative challenge of ozone than normal cells, possibly by way of a less functional glutathione system.

There are many clinical and anecdotal reports,[21,25,27,59] of ozone major or minor autotherapy, at times prescribed on a daily basis for several weeks applied to the treatment of various carcinomatous conditions but with a paucity of controlled data. Several researchers have focused their efforts on using ozone as an adjunct to radiation or chemotherapy.[23]

Summary and Future Directions

Ozone, an allotropic form of oxygen, possesses unique properties which are being defined and applied to biological systems as well as to clinical practice. As a molecule containing a large excess of energy, through incompletely understood mechanisms, it manifests bactericidal, virucidal and fungicidal action which may make it a treatment of choice in certain conditions and an adjunct to treatment in others. Although ozone's medicinal effects were discovered in the 19th century and clinically applied during World War I, equipment capable of purity and reliability of delivery of oxygen-ozone mixtures were not available until the late 1950s. Since then, experience has accumulated for the administration of ozone to humans and animals via a variety of routes, in doses that are both nontoxic and relevant to clinical problems, externally in gaseous form (or in solution) and systemically in blood ozonation.

A review of a large body of literature is presented which describes a spectrum of therapeutic indications. Of these, ozone application for superficial infection, burns, dental and intestinal conditions, and possibly circulatory problems seem to be the most promising. As regards blood ozonation, further research is indicated to delineate the nature of its dynamics and the extent of its effectiveness in (1) the identification of the galaxy of compounds formed in this process which, in view of doses administered, by all evidence, have metabolic, immunological, endocrine and possibly neurological effects; (2) the purification of blood or blood components for transfusion purposes; (3) the inhibition of carcinomas with reference to the types which may be the most susceptible and to its use as an adjunct to radiation or chemotherapy; and (4) the inactivation or the repression of viral diseases with special attention to chronic conditions of the Herpes or Retroviridae (HIV) families.

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