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Ozone in Medicine: Overview and Future Directions

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Abstract

Ozone, a naturally occurring configuration of three oxygen atoms best known for its protective role in the earth's ecological harmony, 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 manifests bactericidal, virucidal and fungicidal actions that may make it a treatment of choice in certain conditions and an adjunctive treatment in others.

Introduction

As early as the First World War, ozone's bactericidal properties were recruited to treat infected wounds, mustard gas burns and fistulas. These first treatment attempts, however, were hampered by technological difficulties. Medical ozone generators have since joined 21st century technology in their capacity to consistently deliver the purest ozone/oxygen mixtures in precise dosages. A critical advance in ozone technology was the development in the 60's of inert materials able to withstand ozone's oxidative challenges thus insuring 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 shed light on defining its clinical applications.

Historical Perspectives

The history of ozone's discovery is closely 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 (Ihde 1964, Partington 1962). 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 repeating these experiments concluded that this odor was due to a gas that he named ozone, from the Greek *ozein* (odorant), and described several of its properties (Schonbein 1868). Many researchers since that time have worked to distill the nature and actions of ozone. Still today, theoretical issues remain regarding its electron dynamics, the varieties of its hybrid forms, and its kinetics. Mariniak and Delarive showed that it is an allotropic form of oxygen, and Mulliken and Dewar clarified its molecular architecture (Razumovskii 1984).

Early in its history ozone was found to oxidize a spectrum of organic compounds and to interact with unsaturated chemical 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 (Razumovskii 1984).

The ability of ozone to destroy toxic or noxious industrial impurities and to inactivate bacterial contaminants in effluents has made it an attractive alternative to chlorination. Wiesbaden in Germany, and Nice in France became the first cities to use ozonation for the purification of their drinking waters (1901), followed by Zurich, Florence, Brussels, Marseille, Singapore and Moscow. Today, there are over 350 municipal water works using ozone as the primary disinfectant in the United States alone, and at least 3000 worldwide.

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 (Rilling 1987). Payr, and Fisch and Wolff (Wolff 1979) were clinician pioneers, and J. Hansler developed one of the first reliable medical ozone generators (Rilling 1987, Hansler 1976).

Physico-Chemical and Biochemical Properties

The oxygen atom exists in nature in several forms: (1) As a free atomic particle, singlet oxygen (O) is highly reactive. It combines with water to form hydrogen peroxide and with hydrogen to form the hydroxyl radical (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 and a density one and a half times that of oxygen. Its molecule contains a large excess of energy (O₃ ? 3/2 O₂ + 143 KJ/mole). With a bond angle of 127°± 3° resonating among several hybrid forms, it is distinctly blue as a gas and dark blue as a solid (4) O₄ is a highly unstable, rare, nonmagnetic pale blue gas that readily breaks down into two molecules of oxygen.



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Ozone is a powerful oxidant, surpassed in this regard only by fluorine. Shonbein, in 1855, discovered that it reacts with ethylene. Exposing ozone to organic molecules containing double or triple chemical bonds yields many complex and as yet incompletely configured ephemeral transitional compounds (e.g., zwitterions, molozonides, cyclic ozonides), which may be hydrolyzed, oxidized, reduced or thermally decomposed to a variety of substances, chiefly aldehydes, ketones, acids and alcohols. Ozone reacts with saturated and unsaturated hydrocarbons, amines, sulfhydryl groups and aromatic compounds. Oxidized by ozone's chemical action are phenols, tetrahydyl lead, oils, soaps, chlorinated alkanes and alkenes, tetrachloroethylene, pesticides, cyanide, iron, manganese, and taste and odor compounds. These pan-oxidizing properties make ozone a superior purifying agent for potable and bathing waters.

Of importance to biological systems is ozone's interaction with tissue (especially blood) constituents. The most studied is lipid peroxidation although interactions occur with carbohydrates, proteins, and glycoproteins. These dynamics are especially relevant for medical applications because some of the most practiced methods in ozone therapy involve exposing ozone to blood.

Since there is a rich variety of lipid components in whole blood, it is of more than theoretical interest to determine the end products of ozone oxidation and the effects they may have on physiological systems and on pathogenic organisms. Cholesterol accounts for 140 to 220 mg/100 ml, of which 60% to 75% are cholesterol esters. Phospholipids account for 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 of blood and the large variety of lipid constituents, the possible end products of ozonation are bountiful (Smith 1987).

Furthermore, blood, in all its complexity, is equipped with systems for buffering lipid peroxidation, including vitamin E, uric acid, and enzymes such as superoxide dismutase, catalase, and glutathione (Meadows 1986, Menzel 1984).

Metabolic and Physiological Effects of Ozone

Most research on ozone's biological effects has 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, ozone and ultraviolet rays, ground level pollution can intensify significantly. The respiratory effects of pure ozone, however, need to be differentiated from those of smog.

The majority of studies performed on animals show substantial interspecies variability in response to inhaled ozone. Due to differences in pulmonary anatomy and physiology, extrapolation to human is problematic. Mice (Mittler 1957) seem to be the most sensitive and birds such as turkeys, the least (Clamann 1960). While overdose is marked by pulmonary edema and hemorrhage, long-term low-level exposure yields contradictory findings. Reported effects include enhanced enzyme activity, as shown by markers of increased glucose utilization (e.g., lactate, carbon dioxide formation, and elevated glucose-6-phosphate dehydrogenase), pointing to ozone enhancement of metabolizing enzymes (Basset 1986).

Humans exposed to ambient ozone (0.24 ppm in room air for two hours) typically develop mildly accelerated breathing with tracheal and laryngeal irritation and chest tightness. Large intersubject response differences are notable (McDonnell 1985). The threshold for significant changes in respiratory compromise ranges from 0.15 ppm to 0.25 ppm (Kulle 1985, Hackney 1977), increasing ozone concentrations yielding corresponding airway hyper-responsiveness and bronchoconstriction. Histological findings points to ciliated cell inhibition and type 2 cell proliferation, increased membrane permeability and variable inflammatory response (Menzel 1984). Reported biochemical alterations include increased oxygen consumption and glucose utilization, activation of NADPH, superoxide dismutase, peroxidase, reductase, and glutathione peroxidase (Melton 1982). Pulmonary effects from ozone in low doses include metabolic activation of lung cells while higher doses produce metabolic compromise. The phenomenon of ozone tolerance or adaptation occurs in both humans and animals (Hackney 1977).

It is clear from the foregoing, that inhaled ozone has both local and systemic repercussions. For this reason, in the methodology of ozone therapy, care is given to avoid the escape of ozone into the treatment area. Contemporary medical ozone generators are equipped to catalytically convert ozone to oxygen after it is administered. Interestingly, some studies point to possible beneficial effects of very low dose ambient ozone in certain pulmonary infections (Dyas 1983, Wolcott 1982).

Research of ozone's effects on red blood cells indicate that at ozone dosage commonly employed in hemotherapy (30 mg/ml), all erythrocyte enzymes and their intermediates remained intact (e.g., hexokinase, aldolase, pyruvate kinase, lactate dehydrogenase, adenyate kinase, glutathione S-transferase, among many others), (Zimran 1999).



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According to other researchers (Rokitansky 1982, Washutll 1979, Viebahn 1994), the direct intravascular injection of pure oxygen-ozone mixtures results in the following responses: (1) An activation of enzymes involved in oxygen radical scavenging (e.g., glutathione, catalase, superoxide dismutase) inducing (2) an acceleration of glycolysis in erythrocytes, resulting in (3) the stimulation of the 2,3 bisphosphoglycerate cycle. The oxyhemoglobin dissociation curve shift releases oxygen to the tissues. Further physiological effects include (4) an enhanced oxidative decarboxylation of pyruvate with the formation of Acetyl-CoA with consequent citric acid cycle activation (5) a direct influence on the mitochondrial transport system with reduction of NADH and oxidation of cytochromes, and (6) an increase in RBC pliability, blood fluidity, and arterial oxygen saturation.

Medical Ozone 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 regulate and monitor the flow of medical grade oxygen through high voltage fields. Incorporated ozone analyzers are capable of guaranteeing precise ozone-oxygen mixtures accurate to within a few micrograms per milliliter. The purity of the oxygen source is emphasized since nitrogen, in the presence of high-energy fields, forms toxic nitric oxides.

Since the half-life of ozone is approximately 45 minutes at 20°C, 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 ozone dose generated is always well below its explosive limit (15 to 20%).

Clinical Indications for External Ozone Gas Application

Historically, medical ozone was first administered by external application to body extremities. A. Wolff in 1915 is credited for using local ozone treatments for infected wounds, decubitus ulcers, and osteomyelitis. Early materials, like rubber, designed to trap ozone around a body part were subject to rapid oxidative destruction. Today, special materials (e.g., Teflon, polyethylene, silicones) allow extremities to be safely encased in a space where a prescribed precise dosage of ozone/oxygen ratio can be administered.

Indication for external ozone applications include infected wounds, poorly healing wounds, diabetic and decubitus skin ulcers, burns, fungal lesions, herpes simplex, herpes zoster, lymphedema, frostbite, radiodermatitis, and gangrene (Viehbahn 1999, Held 1983, Werkmeister 1985, Sunnen 1988). Ozone concentrations are adapted to the changing clinical condition under treatment. External gas perfusions may last from 5 to 60 minutes, with ozone concentrations varying from 0.5% to 5%. High ozone concentrations are used for disinfection and debridement while low concentrations promote epithelialization and resolution (Werkmeister 1985).

Contraindications to ozone treatment are few. They include acute alcohol intoxication, recent myocardial infarction, hemorrhage from any organ, pregnancy, hyperthyroidism, thrombocytopenia, and ozone allergy (Rilling 1987).

Autohemotherapy (AHT)

Whereas it can be readily understood that external ozone applications produce local effects such as disinfection, wound healing, or local circulatory enhancement due to ozone's vasodilatory properties, the technique of introducing ozone into the circulation poses more complex issues. In the technique of autohemotherapy, 50 to 250 ml of blood are drawn, mixed with a prescribed dose of ozone-oxygen and then returned to the patient. Once returned, the ozonated blood is rapidly distributed to all tissues. Clinically, some patients upon receiving their own ozonated blood report a distant background taste of ozone, which may be an indication of its survivability in solution for at least a few seconds.

In hemotherapy, ozone is administered to increase the oxygenation and the red cell fluidity in the treated blood aliquot, and for eliminating the pathogens it may contain. In addition, beneficial systemic immunological and antiviral actions are reported (Vogelsberger 1983; Viebahn 1999; Bocci 2005).

Autohemotherapy has been applied to the treatment of several conditions, including acute and chronic viral infections, some carcinomas, and circulatory disturbances such as diabetes and arteriosclerosis. Ozone-enhanced remineralization of bone has been reported (Riva-Sanseverino 1987). Of interest are the testimonies of some patients, who after receiving 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.

Extracorporeal Ozone Therapy

Another, more experimental and more comprehensive technique of ozone administration makes use of the extracorporeal



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treatment of the entire blood volume using a hollow-fibre oxygenator-ozonizer (Di Paolo 2000; Bocci 2002). All blood and lymphatic fluids are thus interfaced with ozone/oxygen mixtures in this promising approach.

Extracorporeal ozone therapy is ideally suited for the administration of low and very low ozone dosages over prolonged periods of time. This methodology may be best suited for the management of acute viral infections when explosive viremia threatens life, as in avian influenza; or in chronic viral afflictions (e.g., hepatitis C, HIV) during periods of viral recrudescence. Research is needed to determine proper indications and treatment protocols for this innovative ozone methodology.

Direct Intra-arterial and Intravenous Administration

Lacoste first used this method in 1951 for circulatory compromise and possible sequelae such as gangrene. In this technique, up to 10 ml of pure oxygen/ozone is slowly injected directly into an artery or into a vein. Administered properly – and this cannot be overemphasized - embolization does not occur since both gases, unlike nitrogen, are readily soluble in blood. Indications include intermittent claudication, leg ulcers, and incipient gangrene (Rokitansky 1982).

Ozone Insufflation

Payr in 1935 and Aubourg in 1936 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 floral balance disturbed by pathogenic organisms. In a typical treatment for ulcerative colitis, daily insufflations are applied. High initial ozone concentrations achieve hemostasis. Subsequently, low ozone concentrations promote resolution (Viebahn 1994). This technique may have some promise in the treatment of bowel infections associated with AIDS. Microsporidia, tiny intestinal parasites may contribute to AIDS wasting illness, and studies are needed to ascertain the benefits of ozone intervention.

Ozonated Water

Ozone is approximately ten times more soluble in water than oxygen. Mixed into aqua bidestillata (pyrogen free) water, at pH 7 and 20°C the half-life of ozone is approximately ten hours; and at 0°C, 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 it may also be rinsed in conditions such as thrush and periodontal disease, and swallowed to soothe gastritis (Turk 1985). Ozonated water may be 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. Diabetic ulcers, decubitus ulcers, and mycoses are indications for its use [Schulz 1982, Washuttl 1982].

Balneotherapy

Ozonated water infused into warm baths provides stimulation of local circulation and disinfectant action to varicosities. Eczema, skin ulcers, and peripheral circulatory disorders are reported to benefit from ozone balneotherapy (Viebahn 1994).

Blood Purification

Several authors have investigated ozone for sterilizing blood supplies (Wolff 1979, Wehrli 1957). 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 examined 10,000 samples and found no cases of hepatitis transmission (Wehrli 1957). Whether ozone treatment of whole blood could assist in its purification is controversial. While possibly efficacious in neutralizing viral particles suspended in plasma, it is doubtful that retroviruses, once ensconced in the genetic material of blood cells, can be cleared by this method (Chun 1999).

Mechanisms of ozone's bactericidal, virucidal and fungicidal action

Bacteria. Exposed to ozone, bacterial species fare poorly, a fact appreciated since the 19th century. Ozone is a strong germicide needing only a few micrograms per liter for measurable action. At a concentration of 1 mg/L H₂O at 1°C, ozone rapidly inactivates coliform bacteria, staphylococcus aureus, and Aeromonas hydrophilia (Lohr 1984).

The cell envelopes of bacteria are composed of intricate multilayers. Covering the bacterial cytoplasm to form the innermost layer of the envelope is the cytoplasmic membrane, made of phospholipids and proteins. Next, a polymeric layer built with giant peptidoglycan molecules provides bacteria with a stable architecture. In Gram-positive organisms, the peptidoglycan



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shell is thick and rigid. By contrast, Gram-negative bacteria possess a thin peptidoglycan lamella on which is superimposed an outer membrane made of lipoproteins and lipopolysaccharides. In acid-fast bacteria, such as *Mycobacterium*, up to one half of the capsule is formed of complex lipids and glycolipids. The high lipid content of the cell membranes of these ubiquitous bacteria may explain their sensitivity, and eventual demise, subsequent to ozone exposure.

The outermost bacterial layer is the polysaccharide capsule. In many bacterial species, the capsule, by way of its stickiness, enables adherence to host tissues. The capacity of *Streptococcus mutans* to accrete to tooth enamel, for example, is due to its capsular properties.

The most cited explanation for ozone's bactericidal effects centers on disruption of cell membrane integrity through oxidation of its phospholipids and lipoproteins. There is evidence for interaction with proteins as well (Mudd 1969). In one study exploring the effect of ozone on *E. coli*, evidence was also found for ozone's penetration through the cell membrane, reacting with cytoplasmic contents, and converting the closed circular plasmid DNA to open DNA, which would presumably diminish the efficiency of bacterial procreation (Ishizaki 1987). Capsular polysaccharides may be possible sites for ozone action. 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 using ozone at doses prescribed, ozone appears to be toxic to pathogens and not to the patient [Cech 1986].

Viruses. Viruses are parasites at the genetic level, separated into families based on their structures, types of nucleic genome and modes of replication.

Recently, there has been renewed interest in the potential of ozone for viral inactivation *in vivo*. It has long been established that ozone neutralizes viruses in aqueous media and it stands to reason that it would be studied for similar applications in living systems. *In vivo* ozone applications, however, present far greater challenges. Indeed, the technology of medical ozone administration aims to respect the delicate balance of patient safety on one hand and antimicrobial efficacy on the other.

All viruses are susceptible to ozone's neutralizing action. Viruses, however, differ in their relative susceptibility to destruction by ozone. In one study, poliovirus resistance was 40 times that of coxsackievirus. Relative susceptibility in ascending order was found to be: poliovirus type 2, echovirus type 1, poliovirus type 1, coxsackievirus type B5, echovirus type 5, and coxsackievirus type A9. In pure water, at maximal solubility of ozone and room temperature, echovirus type 29 is inactivated in one minute, poliovirus type 1 in two, type 3 in three, and type 2 in seven minutes (Roy 1982). 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 producing replicating dysfunction. Other researchers, in similar experiments, concluded that in ozonation, it is the viral capsid that sustains damage (Riesser 1977). Viruses, unlike mammalian cells, have no enzymatic protection against oxidative stress.

Lipid-enveloped viruses are sensitive to treatment with ether, organic solvents, and ozone, indicating that disruption or loss of lipids results in impaired or destroyed infectivity. Viruses containing lipid envelopes include the Hepadnaviridae (Hepatitis B), the Flaviviridae (hepatitis C, West Nile virus, yellow fever); the *Herpesviridae*, a large family grouping the Simplex, Varicella-Zoster, Cytomegalovirus, and Epstein-Barr viruses; the *Orthomyxoviridae* (avian influenza); the *Paramyxoviridae* (mumps, measles); the *Coronaviridae* (SARS); the *Rhabdoviridae* (rabies); the *Togaviridae* (Rubella, encephalitis); the *Bunyaviridae* (Hantavirus); the *Poxviridae* (smallpox); and the *Retroviridae* (HIV), among others. Indeed, once the virion's lipid envelope becomes fragmented, its DNA or RNA core cannot survive.

The enveloped viruses, adapted to the delicate homeostatic milieu of their hosts are usually more sensitive to all physico-chemical challenges than are naked virions. This has been shown for ozone (Bolton 1982). Although ozone's effects upon unsaturated lipids are one of its best documented biochemical actions, ozone is known to interact with other viral constituents. This becomes relevant when ozone inactivation of non-enveloped virions is considered.

Viruses that do not have an envelope are called "naked viruses." They are constituted of a nucleic acid core made of DNA or RNA, and a nucleic acid coat, or capsid, made of protein. Some non-enveloped viruses include: *Adenoviridae* (respiratory infections), *Picornaviridae* (poliovirus, coxsackie, echovirus, rhinovirus, hepatitis A), *Caliciviridae* (hepatitis E, Norwalk gastroenteritis), and *Papillomaviridae* (*Molluscum contagiosum*). Ozone can interact with viral proteins, their constituent amino acids and lipopolysaccharides. Indeed, when ozone comes in contact with viral capsid proteins, protein hydroxides and protein hydroperoxides are formed and viral demise ensues.



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In summary, ozone's antiviral action in blood may recruit the following mechanisms:

1. The denaturation of virions through direct contact with ozone. Ozone, via this mechanism, disrupts viral envelope lipids, phospholipids and lipoproteins. The presence of numerous chemical double bonds in these unsaturated molecules makes them vulnerable to the oxidizing effects of ozone, which readily donates its oxygen atom and accepts electrons in redox reactions. Broken bonds are thus reconfigured, molecular architecture becomes disrupted, and breakage of the viral envelope ensues. Deprived of an envelope, virions cannot sustain nor replicate themselves.
2. Ozone proper may directly alter structures on the viral envelope that are necessary for attachment to host cells. Peplomers, the viral glycoproteins protuberances that connect to host cell receptors are likely sites of ozone action. Alteration in peplomer integrity impairs attachment to host cellular membranes foiling viral attachment and penetration.
3. Introduction of ozone into the serum portion of whole blood induces the formation of lipid and protein peroxides. While these peroxides are not toxic to the host in quantities produced by ozone therapy, they nevertheless possess oxidizing properties of their own which persist in the bloodstream for several hours. Peroxides created by ozone administration may serve to further reduce viral load.
4. Immunological effects of ozone have been documented. Cytokines are proteins manufactured by several different types of cells that regulate the functions of other cells. Mostly released by leucocytes, they are important in mobilizing immune response. Ozone induces the release of cytokines that in turn activate a spectrum of immune cells. Ozone is reported to be an immuno-stimulant in low doses and immuno-inhibitory at higher levels (Werkmeister 1985, Varro 1974, Zabel 1960). Additionally, ozone functions as a signaling agent by stimulating production of nuclear factor kappa B, interleukin 6, and tumor necrosis factor a. Ozone's capacity for cytokine activation has been amply documented (Bocci 2005).
5. Ozone actions on viral particles in infected blood yield several possible outcomes. One outcome is the modification of virions so that they remain structurally intact yet sufficiently dysfunctional as to be nonpathogenic. This attenuation of viral particle functionality through slight modifications of the viral envelope, and possibly the viral genome itself, modifies pathogenicity and allows the host to increase the sophistication of its immune response. The creation of dysfunctional viruses by ozone offers unique therapeutic possibilities. In view of the fact that so many mutational variants exist in any one afflicted individual, the creation of an antigenic spectrum of crippled virions could provide for a unique host-specific stimulation of the immune system, thus designing what may be called a host-specific autovaccine.
6. An exciting avenue of research suggests that the virucidal properties of antibodies are predicated upon their ability to catalyze highly active forms of oxygen including ozone (Marx 2002; Wentworth 2002). In this model, activated neutrophils provided with appropriate starting materials are capable of generating singlet oxygen, a most powerful oxidant. The singlet oxygen combines with oxygen to form ozone, itself an oxidant, whose electron-extracting capacity is only second to fluorine. It can also combine with water to form the hydroxyl radical (OH) and hydrogen peroxide. Endogenously created ozone thus becomes a fundamental immunological agent for viral inactivation.

Exogenously administered ozone may, based on this model, amplify the efficacy of antigen-antibody dynamics.

Fungi. 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 (Matus 1981). In another study, low doses of ozone stimulated the growth and development of *Monilia fructigena* and *Phytophthora infestans*, while higher doses were inhibitory (Matus 1952).

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.

Warburg in 1925 proposed that tumors have higher rates of glycolysis under aerobic conditions than do nontumor cells. Since then, efforts have been made to test his hypothesis by determining the oxidative conditions which could best enhance cancer treatment strategy. Although his statement has subsequently been amended considerably, there is an evolving body of research centering on the biochemical differences between normal and malignant cells (De Vita 1985, Bocci 2002).

Some tumors have high rates of glucose use and lactic acid production in the presence of oxygen, a reflection of a number of



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possible mechanisms including membrane transport alteration and variations in ATP regulation. Some cancer cell mitochondrial ribosomes have altered structures and function that could diminish their energy producing abilities and compromise their aerobic tolerance (De Vita 1985).

Some authors report a peroxide intolerance in tumor cells. Possessing insufficient catalase and peroxidase enzymes, some cancer cells have difficulty processing peroxides. Exposed to ozone, these cells are said to show a significant decrease in lactate content, indicating that ozone may induce metabolic inhibition in some carcinomas (Rilling 1987, Varro 1974).

In one landmark study, 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 ozone for 8 days). Alveolar adenocarcinoma, breast adenocarcinoma, uterine carcinosarcoma and endometrial carcinoma showed a 40% cell growth inhibition at 0.3 ppm of ozone and 60% at 0.5 ppm. The non-cancerous lung cells were unaffected at these levels. At 0.8 ppm ozone exposure, cancer cell growth inhibition was 90%. Interestingly, it was at this level that the control cell group started to manifest anabolic slowdown. The authors postulate that cancer cells are less able to compensate for the oxidative challenge of ozone than normal cells, possibly by way of reduced functionality of the glutathione system (Sweet 1980).

There are many clinical and anecdotal reports but a paucity of controlled data of ozone hemotherapy applied to the treatment of various carcinomatous conditions (Wolff 1977, Lacoste 1951, Zabel 1960, Wenzel 1983). Several researchers have focused their efforts on using ozone as an adjunct to radiation and chemotherapy (Tietz 1983).

Summary and Future Directions

Ozone, an allotropic form of oxygen, possesses unique properties that are being defined and applied to biological systems as well as to clinical practice. As a molecule containing a large excess of energy, it embodies bactericidal, virucidal, and fungicidal action that 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 One, technologies capable of purity and precision delivery of oxygen-ozone mixtures were not available until the 1960's. Since then, experience has accumulated for the administration of ozone to humans and animals via a variety of routes, in doses that are both safe and relevant to clinical problems, externally in gaseous form and systemically in the process of blood ozonation.

A review of a body of literature is presented which describes a spectrum of ozone's therapeutic indications. Of these, ozone application for external infections is clearly established. These include infected wounds, diabetic ulcers, and burns.

Ozone can be safely administered in techniques of blood ozonation. Ozone hemotherapy is the serial ozonation of blood aliquots. Extracorporeal ozone therapy treats the entire blood and lymphatic systems.

The principal indication for blood ozonation is for the treatment of viral infections. Lipid-enveloped viral organisms are the most susceptible to ozone's oxidative action. This group of viruses is responsible for some of the most challenging diseases facing the world's population.

Possible mechanisms for ozone's antiviral properties are described implicating physico-chemical and immune dynamics. The recent discovery that ozone is produced *in vivo* as a fundamental immunological defense against pathogenic organisms opens exciting conceptual and research directions for the clinical use of ozone in medicine.

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