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Ozone Preconditioning: Waking up the dragon

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It is said that no discovery is complete until its implications have been fully realized. The identification of a previously unrecognized phenomenon says little of its potential effects. What appears as a stroke of good luck can culminate in disaster; misfortune may harbor unimagined potential. Discovery is a double-edged sword that manifests only over time. Nowhere is this aphorism more applicable than in contemporary medical science.

The tried-and-true mode of discovery in 20th century medical therapeutics falls along this line: the beneficial effect of a substance is observed empirically during random testing or, conversely, new compounds are synthesized based on some existing pharmacologic principle; the substance undergoes testing in animals and, if no undesirable consequences ensue, clinical studies in humans are conducted. Ultimately, if the substance passes muster on these counts, it will be approved by some regulatory agency, the FDA for example, for general use in individuals with appropriate medical indications.

In the case of the numerous drug-induced mass tragedies that punctuated 20th century medicine—sulfanilamide, thalidomide, isoproterenol, diethystilbesterol, fenoterol, Fenfluramine-phentermine, cerivastatin, or rofecoxib—the disaster can generally be attributed to insufficient vetting of a substance, malfeasance by the pharmaceutical concern, failure of proper oversight by regulatory agencies or any combination of the three. In such cases completion of the discovery process then occurs at the expense of the public after the substance is in general circulation.

Undoubtedly the most conspicuous exception to this rule of thumb is found in the strange case of ozone, a volatile atmospheric gas, in which every aspect of medical convention and discovery is turned topsy-turvy. From the beginning ozone was labelled as a toxic environmental substance, a conclusion borne out by numerous laboratory and epidemiologic studies. When in excess in atmospheric air ozone produces difficulty in breathing, cough, nasal congestion, tear formation, chest discomfort and, in susceptible individuals, predisposes to asthma attacks, angina pectoris and occasional heart attack. Such effects incriminate ozone as a hazard to human health.

Laboratory studies confirm such effects at the cellular and molecular level. A powerful oxidant, ozone diverts energy intended for cellular use resulting in impaired mitochondrial function, diminished ATP synthesis, production of reactive oxygen species and a host of toxic intermediary compounds. Its mechanism of action has been documented in so many studies in animals and humans over the past century as to galvanize consensus among those familiar with the topic. It is hardly surprising that regulatory agencies seek to restrict atmospheric levels and limit human exposure to its deleterious influences. But as in so many other cases things aren't quite as simple as they first appear.

In the 1970s reports began to surface of paradoxical benefits from small ozone doses administered by various routes that bypass the lungs and, instead, funnel directly into the blood. In the 1980s physicians reported beneficial results with ozone in HIV patients. Later studies indicated

that ozone enhances immune function. The list of disorders that responded favourably to ozone treatment grew dramatically: autoimmune conditions, peripheral vascular disease, fibromyalgia, neurodegenerative diseases, renal and gastrointestinal disorders, various cancers, healing of wounds and more. Recent studies found beneficial effects in Covid-19 pneumonitis.

What is at play in this dramatic and unexpected turn of events? Why has there been such pushback from regulatory agencies like the FDA? And why has organized medicine been so slow to recognize the vast potential of ozone and implement it into its therapeutic regimen? Based on accrued data, this lapse too appears to be playing out at the expense of the public. In this paper we examine the science behind the ozone phenomenon. Emerging recognition of its vast therapeutic potential has been greatly amplified by two seemingly unrelated discoveries in the closing decades of the 20th century.

The first was the discovery of the preconditioning (PC) phenomenon by Murry et al in 1986 which found that one or more applications of 'sublethal' amounts of physiologic stressors like ischemia, hyperthermia, or toxins induce a powerful counter-response that confers body-wide protection to subsequent insults acutely and for up to 72h afterward. The PC phenomenon is now recognized to be the most powerful form of endogenous protection ever discovered. The second linchpin discovery was the recognition of an organized energy field in the blood that originates through the contraction and dilation of the heart. As we will see ozone activates this energy field and asserts its effects via the PC phenomenon.

The Ozone Paradox

In the 1880s, German pharmacologist Hugo Schulz examined the effects of toxic substances on yeast cultures. Using a variety of compounds over a broad range of concentrations, and expecting to find progressive dose-dependent toxicity, Schulz was taken aback to observe that while all agents produced toxic effects at high doses, they paradoxically stimulated fermentation in yeast cultures at low concentrations [1]. Schulz found similar reports in the research literature.

Upon sharing his findings with homeopathic physician Rudolph Arndt, they deduced that such results must be independent of the particular chemical applied and, instead, represent an adaptive response on the part of the organism. Administered toxic substances have more than one effect and act in a biphasic manner: small doses stimulate; large doses inhibit. This axiom came to be known as the Arndt-Schulz Rule.

In the 1930s the Arndt-Schulz Rule came under blistering attack by English pharmacologists and by decade's end had apparently been discredited [2, 3]. Nonetheless a steady stream of reports continued to surface in the scientific literature describing biphasic effects in plants, microorganisms, insects, as well as higher organisms. In the 1940s two investigators described the effect in fungal cultures and renamed it hormesis. Reports continued to indicate that substances possessed both stimulatory and inhibitory effects [4].

In recent decades the dose-response revolution has gathered steam in large part due to the writings of toxicologist Edward Calabrese. Beginning around 2000, he published a series of illuminating papers on hormesis, which document the rise, fall and eventual revival of an excluded perspective. He cites many scientific articles confirming biphasic dose effects as well as offering deep, informed analysis of the historical currents which have shaped its complicated legacy [5-10]. Such paradoxical biphasic effects are seen with ozone.

Rats exposed to higher doses and/or longer periods of ozone developed brain dysfunction manifesting in cognitive and motor impairment. Other reports found that ozone inhalation induced pathological neuronal alterations in the brainstem, basal ganglier and hippocampal regions which would seem to explain the various functional impairments [11-14]. It is well-established that elevated ozone levels in inspired air are associated with increased incidence of ischemic stroke in humans [15-18].

On the other hand, an increasing number of studies support the beneficial role of ozone in the treatment of various neurological conditions. Ozone has been used for decades in acute and chronic neuropathic pain syndromes with reduction in subjective pain scores as well as analgesic requirements [19-28]. Sporadic reports suggest its potential to reduce the size of the ischemic penumbra in acute stroke and thus limit the severity of long-term functional deficits [29-32].

Recent studies point to its clinical utility in neuroinflammatory conditions like multiple sclerosis. In addition to symptomatic improvement effects include reduction of oxidation markers, proinflammatory T-cells and cytokines and increased anti-oxidant levels, regulatory T-cells and anti-inflammatory cytokines [33-38]. While ozone's mechanism of action has been elucidated in great detail the means by which its benefits are conferred remain sketchy. And this is where the PC phenomenon comes into play.

Murry and colleagues executed their original PC experiment in an attempt to determine mechanisms at play in myocardial infarct. They had deduced that infarct must be secondary to either exhaustion of energy reserves or build-up of toxic metabolites. They tested

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whether intermittently reopening the coronary arteries to allow for brief return of blood flow altered the course of cellular injury [39]. In a control group of dogs a coronary artery was clamped for 40 minutes to assess the extent of infarct damage. Another group underwent a series of four 5-minute arterial occlusions interrupted by 5-minute intervals of reperfusion. Afterward the artery was clamped for 40 minutes. To their complete surprise, animals that received PC pulses had only about 25% of damage as the control group. How can this be?

The protection afforded by the PC phenomenon has been substantiated in many human and animal studies. When the PC sequence is applied prior to a prolonged ischemic episode a period of protection ensues that lasts about 2-3h during which ischemia-mediated damage is markedly reduced. Biochemical analysis suggests that PC supposedly slows the rate of ATP consumption, anaerobic glycolysis, lactate accumulation, and development of tissue acidosis. Surprisingly, cardiovascular functions like endothelial dependent vasodilation are preserved and the myocardium becomes resistant to potentially lethal arrhythmias. Researchers are at a loss to explain the various effects but suggest that PC pulses somehow slow the metabolism and diminish energy demand [40-49].

A 1993 study found that preconditioning pulses applied to one vascular territory of the heart protected the rest of the heart from prolonged arterial occlusion [50]. Several years later another study found reduction in myocardial infarct size in rabbits after administration of PC pulses to skeletal muscle [51]. Reports soon followed describing protection in organs besides the heart after PC pulses in distant vascular territories. Remote PC effects involving brain, liver, intestines, kidneys, stomach and lungs were described [52-65].

The PC response originates in the cardiovascular system and blood and spreads throughout the body. PC pulses applied to any vascular bed confer systemic resistance to prolonged ischemia. Remote PC induced by serial inflation-deflation of a blood pressure cuff in the extremities is now used prior to various surgical procedures to limit operative and postoperative injury [66]. Reports suggest beneficial effects are transferable from one animal to another by transfusion of blood or bodily fluids [67-69]. It became recognized that the PC response could be induced by different means other than ischemia: hyperthermia, exercise, cardiac pacing, ethanol, volatile anesthetics, and a host of others including ozone [70-88].

A 1996 study ascribing a complex temporal signature to the PC phenomenon complicated the picture even further [89]. The initial period of heightened resistance to ischemic injury disappears after about 2-3h but then protective effects recur in echo-like fashion about 24h later and persist for up to 48-72h; this is called the second window of protection. Researchers remain baffled as to its basis [90, 91]. As effects are associated with appearance of different mediator substances in the blood it appears to involve gene transcription.

Two reports in 2004 suggested that PC pulses administered after a period of prolonged ischemia, i.e., post-conditioning, delivers cardioprotective effects. Post-conditioning sequences can be applied either locally or at a distance with protective benefit [92, 93]. Another study in 2011 found that remote PC delivered during an ischemic episode conferred neuroprotection [94]. Thus, whether the conditioning sequence is delivered before, during, or after a sublethal injury beneficial effects are potentially conferred [95]. Such events can only be explained on the basis of an infusion of energy reserves into the blood.

PC is now regarded as the most powerful form of body-wide protection. It has been 35 years since its discovery and 10,000's of reports in the literature have detailed its various aspects. Molecular biologists have identified dozens of potential chemical mediators and various mechanisms—heat shock proteins, adenosine, various neurotransmitters, erythropoietin, nitric oxide, oxygen-derived free radicals, ATP-sensitive potassium channels to name a few—but to date no convincing molecular explanation for the PC phenomenon has come to light [96-106].

Calabrese argues that the PC phenomenon and hormesis are one and the same but evidence does not support his claim [107, 108]. That all pharmacologically active substances operate in hormetic fashion does not imply that all agents possess the ability induce PC. Most substances exhibit a characteristic spectrum of dose-dependent side effects and appear to operate in a mechanism quite distinct from PC. What Calabrese and molecular biologists overlook is the energy equation. All molecular substances effect their change within a pre-existing energetic milieu and this is where the next discovery plays a decisive role.

Around the time Murry and colleagues stumbled upon the PC phenomenon the cardiology world was in the midst of a profound paradigm shift. For most of the 20th century the heart had been conceived as a mechanical pump which propelled blood forward through the arteries during the systolic phase of its cycle. Diastole, in turn, was regarded as a period of passive relaxation. In the early 1980s reports surfaced describing negative intraventricular pressures in early diastole which researchers soon realized must account for diastolic filling and the forward movement of blood [109, 110].

A 1986 article in *Scientific American* entitled *The Heart as a Suction Pump* advanced a new model of cardiac function [111]. A spate of articles followed in support of active dilation and by the late 1980s researchers had coined the term 'diastolic dysfunction' to designate a growing number of disease conditions associated with impaired

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outward movement of the ventricle [113, 114]. In the mid-1990s a paper refuted the propulsion theory of heart function [114]. By the 1990s imaging studies described spiral arterial flow currents which can only be explained on the basis of a suction force [115-119].

This concept explains the complex mechanics of the fetal heart: systolic forward force alone is insufficient to convey blood through the fetal circulation, extracorporeally through umbilical cord arteries, placenta, and then back into the fetus in the umbilical vein. From a dynamic perspective, this is impossible without a diastolic suctional force to augment the systolic contribution. Similarly, the diastolic dysfunction described above in adults is seen in the fetus manifesting as abnormal diastolic waveforms seen by Doppler velocimetry. An early diastolic suctional force in the heart has been demonstrated following delivery of the infant [111-115].

Since the introduction of the electrocardiogram in the early decades of the 20th century scientists assumed that electrical currents flowing through the nerves along the outer surface of the heart caused the ventricles to contract despite the fact that the heart possesses intrinsic rhythmicity and continues to function in the absence of nerves. Nor did scientists consider what happens to the electrical currents seen on ECG after they ostensibly induce contraction of the heart. Do they vanish into thin air?

Evidence suggests that electron currents are drawn through the nerves by the contraction of the heart and infused directly into the blood. The excess of negative charge induces formed blood elements like proteins to repel which initiates active dilation during the succeeding diastolic phase. Those familiar with Faraday's Law will recognize that the spiral motion of the blood and its electrical currents generates an electromagnetic field which is distributed to cells and tissues throughout the body. There is not one but two circulations: one of flowing fluids, the other of flowing energy currents [120].

The notion of an organized blood-borne energy field is not new. It was first advanced by Roman physician Galen in the late 2nd century AD and was accepted as fact by physicians for 1500 years until it was arbitrarily discarded by chemically oriented scientists and physicians in the 17th and 18th centuries. In Galen's humoral system of medicine, the energy and nutrient substances needed to drive all bodily functions came from the blood [121].

Deterioration of the heart-blood energy field forms the basis of numerous chronic diseases. A plethora of reports link diastolic dysfunction to coronary artery disease, chronic heart failure and other cardiac conditions; diastolic dysfunction is associated with metabolic syndrome X, first described in the 1980s, and the cluster of associated disturbances including hypertension, insulin resistance, diabetes, and obesity [122, 123]. Equally these chronic diseases reflect impaired energy generation in the blood and, as we will see, it is on this basis that the powerful effects of ozone PC are mediated.

Ozone Preconditioning

Hormesis is not a new concept. Roman poet Marcus Lucan introduced the term *immunis*, meaning exemption from duty or fate, in the 1st century AD when writing of the legendary resistance of the African Psylli tribe to the effects of venomous snakebite. For centuries it was known that exposure to small doses of a toxin confers protection to subsequent larger amounts of it. During the 19th century homeopathic physicians recognized this principle at play in Jenner's introduction of vaccination. But description and explanation are two different things. In PC one comes face-to-face with the dynamics behind this long-established principle. And as in the case of molecular biologists, one cannot explain the PC phenomenon without invoking the presence of an organized energy field in the blood.

PC comprises two opposing aspects: the immediate consequences of the toxic assault and the protective response initiated by the body to counteract its noxious influence. A dramatic display of this PC effect is seen with ozone, possibly the most powerful PC agent yet discovered. Ozone's primary effect is induction of brief oxidative injury, especially on membrane lipids, which impairs mitochondrial energy generation and leads to formation of reactive oxygen and nitrate species which compound cellular injury. Such oxidative insults on the cell machinery trigger release of pro-inflammatory cytokines that elicit an immune response further aggravating cell damage. The cascade of events induces a self-amplifying spiral of deterioration in cells which is then counterpoised by an infusion of energy into the blood resulting in the first window of PC protection.

While ozone's effects are well known, its mechanism of action remains unclear. Ozone, triatomic oxygen, exists in various mesomeric (resonance) states and is 10-15X more soluble in water than is diatomic oxygen. Once in contact with bodily fluids it immediately solubilizes and effects are likely mediated via an induced resonance state in water, which accounts for the body-wide actions. While diatomic oxygen is an avid electron scavenger, dissolved ozone is an *uber* energy sink that draws electron-equivalents from biomolecules leaving them in an energy-poor oxidized state. This results in conversion of polyunsaturated fatty acids in plasma into various lipid oxidation products: lipoperoxyl radicals, hydroperoxides, malonyldialdehyde, and 4-hydroxy-2,3-transnonenal (HNE) and more [124-127].

Molecular biologists claim that lipid oxidation products, especially HNE, pass throughout the body and act as

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messenger substances to turn on gene function and transcription of biomolecules which then counteract the injurious effects of ozone. But this explanation makes no sense. Ozone induces profound depletion of intracellular energy reserves with resultant mitochondrial dysfunction and build-up of free radical species. Given that gene transcription and protein synthesis are energy-requiring, from where does the energy come to carry out such constitutive processes? At this point the molecular account falls apart [128-131]. The PC response begins above the tissue level and has its origins in the blood.

Blood cells, in particular erythrocytes (RBCs), are the first to experience the oxidative effects of ozone and to mount a response. RBCs, highly metabolically active, form a large part of the intravascular compartment with an estimated mass of up to 2.3 kilograms. Upon contact with ozonated water, RBCs undergo a transient dose-dependent decrease in energy flux, estimated to be in the 5-25% range over a period of 15-20 minutes, and then respond with a rebound surge in energy release along with outpouring of antioxidants. Ozone induces up-regulation of glycolytic enzymes in RBCs with activation of the Krebs cycle, enhanced ATP synthesis, and production of NADPH reducing equivalents which spill into the blood and neutralize the oxidizing effects of ozonated water [132-136].

Heightened energy output by the RBC mass translates directly into increased blood flow and energy delivery to peripheral tissues. RBCs possess the enzyme nitric oxide (NO) synthase and generate large amounts of NO in response to oxidative stress that not only increases RBC hardiness and deformability but interacts with endothelial-generated NO to maintain active vasodilation (a reliable proxy for blood energy content) [137-148]. Ozone-related oxidative stress triggers activation of hypoxia inducible factor-1 (HIF-1) which, in turn, augments release of vascular endothelial growth factor (VEGF) and erythropoietin (EPO) which stimulate angiogenesis, blood flow and oxygen delivery to peripheral tissues [149].

It is clear that the first phase of the PC response, aimed at generating increased blood energy levels, is responsible for orchestrating subsequent events at the cellular level. Energy currents, carried in the interstitial fluid space, enter cells via ion channel mechanisms and, in short order, enhance mitochondrial function and intracellular energy metabolism as well as inducing a plethora of genes that actively counteract oxidative stress. Equally clear is that the second window of protection is mainly driven by events at the cellular level as a result of gene induction. Critical response pathways include nuclear factor erythroid 2-related factor 2 (Nrf2) and the heme oxygenase-1 enzyme (HO-1) system.

The powerful antioxidant and anti-inflammatory effects unleashed throughout the body by low dose ozone administration are mediated through activation of the transcription factor Nrf2. Nrf2, master regulator of redox balance, binds to over 200 different genes, known as the antioxidant response element (ARE), and effects transcription of cytoprotective substances like heat shock proteins, antioxidant and detoxification molecules, enzymes involved in synthesis of glutathione, a host of growth factors like VEGF and EPO, and more. The Nrf2-driven battery of gene products also effects breakdown and/or refolding of misfolded proteins, DNA repair, mitochondrial rebuilding, autophagy regulation, as well as intracellular metabolism. Impaired Nrf2 function is a hallmark of many chronic disease conditions [150-156].

This robust counter-response is facilitated by disassembly of the very cell from which the PC phenomenon originates: the RBC. Since its discovery in 1968 it was widely assumed that HO-1 was involved solely in haemoglobin degradation and bilirubin metabolism but by the late 1980s, it was recognized that it is induced by factors that produce oxidative stress like ischemia, hyperthermia, endotoxins, heavy metals, and that it plays a role in the PC response and cell homeostasis. HO-1, with strong anti-inflammatory properties, regulates processes like apoptosis, cell proliferation, and angiogenesis. And bilirubin, long thought to be an inactive haemoglobin breakdown product, is now known to be a potent antioxidant [156-167]. It all comes full circle in the blood.

One of the most striking downstream effects of ozone PC is modulation of the inflammatory response. Intracellular inflammation is mediated by the NLRP3 inflammasome, a multiprotein complex that integrates stress signals from the extracellular fluid space, so-called pathogen- and damage-associated molecular patterns, and internal stress signals such as reactive oxygen species related to mitochondrial dysfunction. Stress signals lead to NLRP3 activation with release of proinflammatory cytokines IL-1β and IL-18 and caspase-1 dependent apoptosis (programmed cell death). Ozone PC asserts anti-inflammatory and anti-apoptotic effects via suppression of NLRP3 inflammasome activity. This effect can only be explained by the direct infusion of energy currents into mitochondria. Since abnormal inflammasome activation is a prominent feature of various chronic conditions like Alzheimer's, autoimmune disorders, cardiac and renal disease, as well as acute inflammatory syndromes like Covid-19, it has been suggested that ozone PC could modulate disease activity in these circumstances [168-183].

Ischemia-Reperfusion Injury

Given the presence of a blood-borne energy field that drives all functional processes in the body, it stands to reason that oxidative injury and its deleterious consequences, or allied conditions like inflammation,

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must represent primary energy deficiency states. Equally, associated symptoms, the chest pain of angina pectoris or neurologic deficits of stroke for example, must be conceived along similar lines. To better understand the dynamics of the PC-associated corrective physiology we examine another common and unexplained phenomenon known as ischemia-reperfusion injury (IRI).

IRI, like PC, has been a topic of great interest in recent years. Reperfusion injury refers to a cascade of catastrophic events set into motion by impaired energy dynamics which arise because of attempts to intervene in dire clinical situations like myocardial infarct, stroke, or organ failure. In all cases, whether as a consequence of angioplasty, thrombolysis, surgical bypass, or transplantation, a prolonged period of flow interruption between the vascular compartment and affected organ had been present and, upon reestablishment of flow, a cascade of adverse events ensues. While the cellular and molecular events related to IRI vary from organ to organ, underlying dynamics are the same. The primary dysfunction involves a maladaptive interplay between the vascular and intracellular fluid compartments [184-191].

The events associated with IRI are exactly those which PC is known to prevent: cell death, disruption of tissue viability and architecture, accumulation of fluid and/or blood in the tissue spaces, and loss of organ function. There are localizing biochemical abnormalities depending on which organ is affected. In the heart arrhythmias and contractile dysfunction often occur. The spiral of deterioration begins after blood flow has been re-established and, depending on the severity of injury, evolves over hours to days. IRI is said to occur in about 20-60% of rescue attempts depending on the type of intervention, involved organ, and preexisting status of the patient. The appearance of IRI counteracts any intended benefit of the procedure and, moreover, may precipitate organ failure or death.

IRI was first described in 1960 after prolonged coronary artery ligation in dogs [192]. Contrary to expectations, reperfusion seemed to accelerate the extent of heart damage. Histologic changes after 30-60 minutes of IR were similar in severity to those observed after 24 hours of permanent occlusion. For decades it remained controversial whether reperfusion of a blocked vessel caused tissue injury. Evidence now indicates it promotes additive damage upon pre-existing ischemic injury. There are no reliable pharmacologic therapies by which to lessen its effects.

In a 2005 study, after stents were deployed across occluded coronary artery segments, researchers applied a post-conditioning sequence using repetitive inflation-deflation cycles with a coronary angioplasty balloon and observed a 36% decrease in the size of the affected area [193]. Such results indicate that the effects of IRI can be mitigated. It also points to the fact that the beneficial effects of PC and the detrimental effects of IRI revolve around a single primary phenomenon: the disposition of energy. Many studies substantiate the effects of ozone PC in preventing or ameliorating IRI-induced tissue injury [194-224]. Studies support the equivalency of ozone PC and ischemic PC [225-226].

The distorted dynamics of IRI can, once again, be understood by distinguishing between events arising from the primary oxidative injury and corrective attempts originating in the arteries and blood. Once arterial occlusion occurs cells shift to anaerobic energy metabolism leading to intracellular acidosis and free radical generation. Given the inefficiencies of such pathways the longer the duration of ischemia the greater the extent of cell damage. Once blood flow into the ischemic zone is re-established the metabolism shifts rapidly in the opposite direction, from anaerobic back into aerobic pathways, often with disastrous consequences.

As oxygen/energy diffuses into cells there is rapid reversal of acidosis with elevation of pH and corresponding shifts in ion currents. But incomplete reduction of oxygen inside cells persists and produces more free radicals that overwhelm antioxidant pathways and further aggravate cell injury. Reactive oxygen species interact with lipids and proteins to generate toxic oxidative products that compound injury. Progressive deterioration of electrochemical gradients across cellular and mitochondrial membranes eventually leads to cell death. Events at the cellular level are only part of the chaos.

As flow returns to the energy-starved tissues a host of blood-borne processes are set into motion that exacerbate the situation. Endothelial cells lining the previously occluded arterial segments resume function and vascular permeability increases to allow passage of immune cells and mediator substances into tissues surrounding the infarct. Immune cells release more cytokines intensifying inflammation. Neutrophils and endothelial cells produce even more free radicals, vasoactive substances and adhesion molecules that worsen effects. The final insult of IRI is microvascular obstruction with stasis of blood flow, the so-called no-reflow phenomenon, in which flow into the ischemic zone ceases altogether due to adhesion of blood elements, vasoconstriction of arterioles, and collapse of the capillary bed due to interstitial edema [227].

The most significant determinants of IRI are duration of tissue ischemia [228-230] and the pre-existing state of the cardiovascular system [231-235]. IRI is more likely to occur and to be more severe in conditions like diabetes, hypertension, heart failure, the metabolic syndrome, as well as with increasing age, i.e., the same conditions in which PC is blunted or absent.

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The most consistent finding in IRI is microvascular dysfunction [236-244]. NO is a proxy for energy flux through the blood. Multiple reports link diminished NO with impaired dilation [245, 246]. Decreased NO levels correlate with vasoconstriction during reperfusion [247]. But while mediating vasodilation, in the presence of extensive tissue injury NO serves as a source of free radicals which cause further damage [248-250]. During IRI there is disturbed endothelial function involving all small blood vessels—arterioles, capillaries and venules—with impaired dilation and outward passage of fluid and immune cells along with decreased reabsorption of interstitial fluid by post-capillary venules. Such reports point to a distinct functional layer centered in the vascular compartment mediated by dilation, contraction and the flow of energy.

The detrimental consequences of IRI, like the beneficial effects of PC, are distributed throughout the vascular compartment: organ failure at one site can induce remote organ injury. A 2000 study found that prolonged intestinal ischemia with IRI induced microvascular dysfunction in the lungs with impaired alveolar-capillary functions and pulmonary hypertension [251]. Another study produced acute lung injury in rats by prolonged cross-clamping of the abdominal aorta [252]. Affected animals showed increased microvascular permeability and elevated pro-inflammatory cytokines. In a 2006 study IRI in the liver was associated with acute lung injury with alterations in NO levels and inflammatory cytokines [253]. IRI in the intestines triggered liver dysfunction with accumulation of leukocytes and inflammatory injury [254]. Another report found that IRI in the liver induced cardiac dysfunction [255]. All these adverse consequences are triggered by dysfunction originating in the energy field.

Microvascular dysfunction associated with IRI is prevented with preconditioning or lessened by postconditioning [256-261]. By 1993 evidence suggested that PC induced tolerance to the effects of IRI [262]. A 1994 study found that ischemic PC protected against coronary endothelial dysfunction associated with IRI [263]. Similar results were reported in 2003 [264]. Ischemic PC preserves intracellular ATP, enhances functional recovery, and coronary reflow during reperfusion [265]. A 2017 study found that remote PC protects against liver IRI through a NO-mediated mechanism, implicating an influx of energy into the vascular compartment [266]. Beneficial effects of ozone PC in experimentally-induced IRI have been shown in heart, lung, liver, kidneys, intestines, and ovaries.

How are all these diverse effects orchestrated unless influenced by a common effector substance? The conclusion is inescapable: PC and IRI are two sides of the same coin, their opposing effects mediated by the disposition of energy in the blood and interstitial fluid space. No definitive answer is to be found in the maze of cellular and molecular pathways.

The Case for Ozone

Having examined ozone PC we can distill principles with regard to its mechanism of action and speculate on various disease states that might be responsive to its effects: by inducing oxidative stress in RBCs it triggers a surge of energy in the blood which passes through the interstitial fluid space, across cell membranes, and into the cytoplasm where it directly stimulates mitochondrial metabolism and activates Nrf2, the transcription factor responsible for switching on hundreds of genes involved in the counter-response. Ozone PC induces a shift from anaerobic to aerobic metabolism, triggers release of free radical scavengers, shuts off pro-inflammatory cytokine signals, quells the immune response and, finally, activates intracellular repair and upbuilding processes. Quite an impressive résumé.

Accordingly, if we compile a list of candidate conditions for ozone PC, we would seek those associated with mitochondrial dysfunction and oxidative injury, those with pro-inflammatory cytokine signatures, and those with functional and symptomatic deficits attributable to defective energy generation. As it happens, that list is quite long and comprises many of the most commonly encountered entities, both acute and chronic, seen in modern clinical practice. And, unfortunately, that expansive list is closely linked to the failure of 20th century medical science to address energy dynamics in the blood.

Over the past 40 years there has been a global explosion of chronic conditions unparalleled in recorded human history: diabetes, obesity, hypertension, the metabolic syndrome, chronic organ failure syndromes involving heart, kidneys and liver, autoimmune disorders, neurodegenerative diseases like Alzheimer's, Parkinson's, Huntington's and amyotrophic lateral sclerosis, a host of chronic pain syndromes, chronic asthma and allergic conditions and a litany of others. Some regard this epidemic of epidemics as the fallout of industrialization, others as the human accompaniment of climate change. In any event, medical science, to date, is neither able to prevent nor alter their progression. Not only is ozone PC effective in a wide range of chronic disease states but in acute infectious conditions like Covid-19.

A 2019 review of ozone treatment in acute infectious disease concluded that it is effective in either adjunctive or stand-alone modes. Ozone has virtually no side effects and does not induce microbial resistance patterns like pharmacologic therapies [267]. Numerous studies affirm ozone's efficacy and safety in Covid-19 disease [267-281]. Thorp et al. describe mechanisms by which ozone therapy affects Covid-19 outcomes: increased antioxidant production, induction of Nrf2- and HO-1-mediated nuclear mechanisms, down-regulation of pro-inflammatory immune pathways, direct toxic viral

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effects, inhibition of viral replication and increased blood and tissue oxygenation [279]. Various reports suggest that ozone's capacity to stimulate immune function, modulate inflammation and suppress viral activity augur a whole new therapeutic paradigm [280].

Ozone therapy reduced viral titers and improved clinical symptoms in Covid-19-infected ICU patients [280]. Other studies found that ozone shortened time-lines for clinical improvement [281]. Since ozone confers protection against organ-injury in ischemia-reperfusion injury it only stands to reason that it should prevent or mitigate multi-system organ failure associated with advanced Covid-19 infection if administered in a time-sensitive manner. Given its widespread availability and negligible cost it is utterly baffling why medical scientists failed to implement ozone therapy during the Covid-19 pandemic; ozone and drugs like hydroxychloroquine, ivermectin, and others have been widely used to effectively treat Covid-19 in outpatient settings. Undoubtedly such a strategy would have saved countless lives. It is predictable that this catastrophic oversight will become the subject of great controversy in coming years.

In that autoimmune disease is defined by chronic recurrent inflammatory episodes involving organs and tissues and characterized by similar dynamics as acute inflammation, i.e., activation of the immune system, elevated levels of pro-inflammatory cytokines, mitochondrial dysfunction and oxidative stress at the cellular level, it would be expected that they too would be ideal candidates for ozone PC [282-291]. A handful of clinical reports confirm its efficacy in multiple sclerosis with down-regulation of the pro-inflammatory state and amelioration of oxidative stress [33-38][292-294]. Similar results have been obtained in laboratory experiments with animal models of rheumatoid arthritis and psoriasis [282-287], and with fibromyalgia [295-301]. Although data is limited, given the presence of mitochondrial dysfunction, oxidative injury, and inflammation in affected neuronal populations in the neurodegenerative disorders [302-305], it would seem that these conditions too would be suitable candidates for ozone PC.

In the previous section we described the powerful effects of PC in preventing or mitigating ischemia-reperfusion injury in various organs including the kidneys, heart, liver and lungs suggesting the potential of ozone therapy in stabilization or reversal of organ failure syndromes. Many studies document the benefits of ozone PC in improving kidney function in a wide range of pathologic states [175][306-320]. Ozone reduces lithotripsy shock wave therapy-induced renal injury [333]; reduces renal inflammation [335], reduces inflammation and renal injury in acetaminophen-induced nephrotoxicity [313]; improves acute nephrotoxicity induced by cisplatin [319], and; attenuates contrast-induced nephropathy [311].
By the same token the protective effects of ozone PC on liver function in ischemia-reperfusion injury suggest its potential in the treatment of various chronic hepatic conditions that to date are largely refractory to current medical therapies like non-alcoholic fatty liver disease, chronic hepatitis and early forms of cirrhosis [321-327]. The incidence of fatty liver disease has exploded in recent decades and it is now a leading cause of hepatic failure and subsequent transplantation. Ozone has been used successfully in a large number of infectious diseases and has been shown to significantly reduce viral loads in Covid-19 as noted above but is also effective in other viral infections including hepatitis C, hepatitis A, and HIV [267][321-326].

A similar argument can be made for its use in the global epidemic of chronic heart failure [329-331], a leading cause of hospitalization in people over sixty years of age. No pharmacologic treatments prevent the insidious and progressive deterioration of heart function in those affected. Given that oxidative stress and mitochondrial dysfunction drive airway inflammation in chronic obstructive pulmonary disease, it seems that ozone PC could play a role in mitigation of pulmonary symptoms in such cases [331, 332].

The explosion of diabetes and the metabolic syndrome over the past four decades has radically changed the health care landscape and the need for new, effective and low-cost treatments has never been greater. Undoubtedly diabetes and the metabolic syndrome originate in the blood as a result of deterioration of its energy field. It is well-known that the PC response is blunted or absent in diabetes and the metabolic syndrome. To our knowledge no studies have directly examined the effect of ozone PC on the underlying disease conditions but multiple reports describe beneficial effects on diabetic foot ulcers and skin wounds which are often refractory to current therapies.

Diabetic ulcers, now seen with increasing frequency, are multifactorial in nature and attributable a host of overlapping factors like coexisting vascular disease, peripheral neuropathy, immunologic abnormalities and superimposed infection. Multiple reports document beneficial effects of ozone therapy on both diabetic and non-diabetic wound healing [333-343]. Ozone promotes healing of diabetic ulcers by modulating all the various contributing factors: enhancing blood flow through nitric oxide induced endothelial dilation, increasing energy flow through peripheral nerves, shifting the immune response toward anti-inflammatory pathways and curbing infection. Lesions are treated with topical ozonated oils, ozone 'tents' and intravenously [344-348].

Ozone PC has been used to treat a wide array of acute and chronic skin wounds beyond diabetic ulcers including bed sores, post-traumatic ulcers, burns, chronic viral infections like human papilloma virus and herpes, vaginal infections related to candida, trichomonas and chlamydia

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overgrowth, rectal abscesses and fistulas, as well as oral aphthous ulcers [344-348]. In their systematic review of ozone treatment in chronic wounds Fitzpatrick et al. found significant improvements in healing and wound closure [344]. In other studies using animal models researchers found increased numbers of fibroblasts and collagen deposition as well as humoral factors like VEGF and transforming growth factor- β suggesting accelerated healing responses [343, 346].

An increasing number of reports document the effectiveness of ozone PC for pain relief in a variety of chronic conditions including low back pain related to disc herniation, degenerative disc disease, sciatica, failed back surgery, as well as post-traumatic, inflammatory, and degenerative joint pain [19-28][349-366]. In such cases ozone has been injected directly into the disc space, neural foramen or joint capsule. In a large outcome study of 2900 patients with lower back pain and sciatica, Muto et al. [365] found that intra-discal and intra-foraminal ozone administration was a safe and efficacious means of treating low back pain. Other studies suggest that symptom relief with ozone was greater than with conventional steroid injections.

In these various chronic pain conditions ozone PC appears to assert its effects through the same means we have already highlighted: enhanced RBC-driven generation of blood-borne energy, increased endothelial-dependent vasodilation and blood flow into the microcirculation, increased oxygen delivery to the tissues, optimization of mitochondrial function with reduction of intracellular stress, and down-regulation of inflammation. The diminished pain perception reported in so many studies can only be attributed to increased energy currents through sensory nerves. On what another basis can this be explained?

The great advantage of ozone lies not only in its ability to trigger energy generation in the blood but in its simple means of production and ridiculously low cost. Just as early scientists scented its presence in the air following lightning strikes, ozone can literally be produced anywhere there is an oxygen source and an appropriate voltage gradient. Its ease of administration and wide variety of potential routes puts many pharmacologic substances to shame: intramuscular, subcuticular, intra-articular, direct intravenous injection, infusion of ozonated-saline, rectal / bladder / vaginal insufflation, trigger point injections, and others [19-28][327-348] [267][295][305].

In addition to its remarkable and durable track record in improving clinical and laboratory parameters in a wide range of acute and chronic disease, ozone has been shown in many clinical studies to have virtually no side effects when administered along established dosing guidelines. It is not hyperbole to say it is far safer than most over-the-counter medicines now available. Given the overwhelming evidence it is not only bewildering but profoundly distressing to observe the numerous attempts in recent years by various oversight agencies to restrict and suppress the use of ozone by health practitioners and the general public as a preventive and therapeutic modality [369-376].

This is particularly relevant given a 2016 study by Makary and Daniel [377] in *BMJ* which found that medical errors in US hospitals accounted for approximately 252,000 deaths annually making it the third leading cause of death. Another epidemiologic study reported by Lazarou et al. [378] in *JAMA* suggests that drug-related deaths may account for up to 50% of this burden. Along these lines we would be remiss if we failed to point out that since the beginning of the 20th century when the modern therapeutic era was inaugurated medical science has yet to cure a single class of disease. Ozone PC may be its last chance to finally get things right.

Paradigm Shift

In his ground-breaking work *The Structure of Scientific Revolutions* (1962) science historian Thomas Kuhn points to an under-appreciated aspect of experimental science: as discoveries are made and new facts come to light, the nature of scientific knowledge must change in accordance with those new facts. Science is fundamentally an evolutionary (and revolutionary) undertaking. Kuhn coined the term 'paradigm' to refer to an explanatory theory and its allied methods and practices. The entire history of the experimental sciences is little more than a series of boom-bust cycles characterized by the rise and fall of successive paradigms. The collapse of an existing paradigm is always heralded by its inability to explain the nature of new facts.

Since the beginning of the 20th century medical science has based all its theories on data derived from the molecular and cellular layers of process. During this time causal explanations have come and gone with striking frequency because molecular and cellular processes are not the only events that transpire inside the body. Molecular and cellular accounts describe but do not explain. The only convincing explanation for the described phenomena is the presence of a blood-borne energy field.

The discovery of the primacy of the diastolic phase of the cardiac cycle (and collapse of the systolic-based heart model) along with the recognition of the preconditioning phenomenon in the 1980s upended the 20th century molecular-cellular paradigm. The subsequent recognition of ozone as the most powerful preconditioning agent yet discovered was only the straw that broke the camel's back. In this sense we can say that the current biomedical paradigm no longer exists as a conceptual reality nor does it have therapeutic relevance.

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The new blood-borne energy-based dynamic paradigm and its allied concept of preconditioning with substances like ozone must now come to the forefront and not only replace the decayed molecular-cellular paradigm but attempt to repair and reverse the incalculable damage inflicted by this obsolete perspective. The king is dead, long live the king!

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