

Use of Free Radicals and Antioxidants in Inflammatory Processes of Animals

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Abstract The inflammatory process is complex and the role of free radicals and antioxidants can be found in each part of it, such as the hemodynamic and permeability changes, the metabolism, and the function of the cells involved in the course of events. The main purpose of the present review is to mention the most common inflammatory processes in animals, the role of free radical formation in these, and the use of antioxidants against their detrimental effects. As with severely increased oxidative stress, decreased free radical formation can cause severe diseases. Hyperbaric oxygen gives an option to overcome the disorders caused by decreased oxidative stress response which is important in the bacterial killing mechanism and wound healing. Endotoxemia, systemic inflammatory response syndrome, in its complexity causes severe deterioration of the organism due to oxidative stress. Various antioxidants can be used to prevent the severity, such as superoxide dismutase (SOD), alpha-tocopherol, glutathione and its precursors, ascorbic acid, adenosine, lactoferrin, and carotenoids, thiols, ebselen, xanthine oxidase inhibitors, inhibitors of phagocyte function, iron ion chelators, and probucol, *N*-acetylcysteine, and 21-aminosteroids. Among pulmonary and other airway inflammatory diseases recurrent airway obstruction of horses causes severe oxidative damage. Apart from the well-known antioxidants, it seems that another antioxidant taurine, via *N*-chlorotaurine formation may protect the lung from oxidant-induced injury. This session contains more data of oxidative stress and possible antioxidant therapeutic advances in selective animal inflammatory diseases, such as kidney disease, gingivitis, uveitis, cataract, dermatitis, osteoarthritis, synovitis, pancreatitis, hepatitis, colitis and giardiasis, encephalopathy, neuritis and spinal cord injury, and bovine mastitis.

Keywords Colitis • Gingivitis • Hepatitis • Hyperbaric oxygen therapy • Inflammation • Mastitis • Neuritis and spinal chord injury • Osteoarthritis • Pancreatitis • Recurrent airway obstruction • Synovitis • Systemic inflammatory response syndrome

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Inflammation is one of the most important and most useful of our host defense mechanisms, and without an adequate inflammatory response, none of us would be living.

“*Quae medicamenta non sanat; ferrum sanat. Quae ferrum non sanat; ignis sanat. Quae vero ignis non sanat; insanabilia reportari oportet* (Those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable)” [47]. As Hippocrates (460–370 BC) described in his aphorism, he believed that any disease could be cured by heat: burning heat and heat as both cause and consequence of inflammation. In Latin *flamma* is the light of fire. It is also one of the most common means whereby our own tissues are injured. The word inflammation itself literally means a “burning”. The Roman Cornelius Celsus formulated his famous “cardinal signs” of inflammation: calor, rubor, tumor, and dolor. That means heat, redness, swelling, and pain. To this classic list of four signs must be added *functio laesa* or loss of function. This fifth sign is often attributed to Galen (AD 130–200), but it really originated with Rudolf Virchow (1821–1902), the father of modern pathology.

The process is complex and the role of free radicals and antioxidants can be found in each part of it such as hemodynamic and permeability changes, the metabolism and function of the cells involved in the course of events. The main purpose of the present review is to mention the most common inflammatory processes in animals, the role of free radical formation in these, and the use of antioxidants against their detrimental effects.

The most important direct effect of free radicals is found in the microbicidal mechanism. There are also various free radical-dependent systems involved in the formation of cytokines, inflammatory mediators, and cellular functions (i.e., platelets; see, for review [130]). Reactive oxygen species (ROS) are involved in wound healing and tissue repair mechanisms [10]. Although the synthesis of inflammatory mediators is a free radical-producing mechanism, the production of stress-induced anti-inflammatory hormones in the adrenal cortex is also a free radical-mediated process, and antioxidants can inhibit these mechanisms [6, 125].

Oxygen-Dependent Killing Mechanisms

The purpose of bacterial phagocytosis is to kill and degrade bacteria. Two different killing systems are recognized: oxygen-dependent and oxygen-independent killing systems. There are two types of oxygen-dependent killing systems known: the so-called oxygen radical system and the myeloperoxidase–halide system [12].

During phagocytosis, neutrophils show a burst of metabolic activity, characterized by a two- to threefold increase in oxygen consumption, an increase in the formation of superoxide anion (O_2^-), hydroxyl anion (OH^-), and hydrogen peroxide (H_2O_2), and an increase in cyanide-independent oxygen uptake and the amount of glucose metabolized by means of the hexose monophosphate shunt (HMPS; Stahelin 1957) [118].

The decrease of this process leads to severe microbial infections. Some hereditary defects have also been reported. The functional defects may be associated with morphological abnormalities, such as in Chédiak–Higashi syndrome, or not associated with morphological changes of neutrophils, such as in chronic granulomatous disease and granulocytopeny syndrome.

An oxygen-dependent killing mechanism is effective against microbes, but this mechanism is responsible for the harmful effects of inflammation. Experimental studies suggest that neutrophil-derived oxygen metabolites contribute to the development of tissue injury associated with a variety of disease states, including emphysema, myocardial infarction, adult respiratory distress syndrome, immune complex-mediated vasculitis, and rheumatoid arthritis [28]. Local inflammatory processes can lead to systemic inflammation and free radical and antioxidant changes can also be dispersed.

“Altera manu fart aquam, altera ignem (One hand carries water, the other fire).” According to this old Latin phrase, one process can lead to both beneficial and harmful processes. In addition to the harmful effects, free radicals produced by neutrophils are essential for the proper microbicide effect, but it has to be mentioned that the oxidative burst is sometimes exaggerated. Increasing oxidative burst activity is of great importance in conditions of decreased function, such as necrotizing fasciitis, or lower extremity wounds [27, 74].

Hyperbaric Oxygen in Therapy

Hyperbaric oxygen (HBO) therapy can be essential to enhance microbial killing; it is worth mentioning some details about HBO therapy in general, the clinical benefits and side effects. This session about HBO therapy is based on Slovis’ [114] paper with modifications. “The art of healing comes from nature, not from the physician. Therefore the physician must start from nature, with an open mind” (Paracelsus, Philippus Theophrastus Aureolus Bombastus von Hohenheim, 1493–1541) [90]. HBO therapy is a typical practical achievement of the Paracelsus theory. One of the most essential elements in nature is oxygen.

HBO therapy involves intermittent inhalation of 100% oxygen under a pressure greater than 1 atm [29]. Increasing pressure in HBO therapy is often expressed in multiples of atmospheric pressure absolute or atmospheres absolute (ATA); 1 ATA equals 1 kg/cm² or 735.5 mm Hg. Most HBO treatments are performed at 2–3 ATA. In air embolism and decompression sickness, where pressure is crucial to the therapeutic effect, treatments frequently start at 6 ATA [34]. This additional pressure, when associated with inspiration of high levels of oxygen, substantially increases the level of oxygen dissolved into blood plasma. This state of serum hyperoxia is the second beneficial effect of HBO therapy [32].

Hyperoxia at sea level in room air means that approximately 97% of hemoglobin is saturated with oxygen (19.5 vol% oxygen, of which approximately 5.8 vol% is extracted by tissue). The amount of oxygen dissolved into plasma is 0.32 vol%.

An increase in pO_2 has a negligible impact on total hemoglobin oxygen content; however, it does result in an increase in the amount of oxygen dissolved directly into the plasma. With 100% inspired oxygen the amount of dissolved blood plasma oxygen increases to 2.09 vol%. At 3 ATA plasma contains 6.8 vol% oxygen, which is the level equivalent to the average tissue requirements for oxygen. Thus, HBO treatment could and has sustained life without oxygen bound to hemoglobin [13]. The cardiovascular effects of HBO include a generalized vasoconstriction and a small reduction in cardiac output [99]. This ultimately may decrease the overall blood supply to a region, but the increase in serum oxygen content results in an overall gain in delivered oxygen. In conditions such as burns, cerebral edema, and crush injuries, this vasoconstriction may be beneficial, reducing edema and tissue swelling while maintaining tissue oxygenation [85]. Hyperbaric or hyperoxic or both conditions may affect the disposition of drugs by (1) changes in the catalytic activity of drug-metabolizing enzymes, (2) hemodynamic changes, and (3) changes in membrane permeability, affecting drug distribution.

In isolated microsome preparations from rat liver, the metabolism rate of aniline, but not of amidopirin, is reduced by hyperoxia. In vivo, the clearance of salicylic acid is enhanced in the dog at 2.8 ATA and 100% O_2 , but not at 6 ATA and air, for reasons that are still unknown. The disposition of theophylline, pentobarbital, or pethidine is not affected in dogs by hyperbaric or hyperoxic conditions.

In human volunteers, hyperbaric or hyperoxic or both conditions do not affect the disposition of gentamycin (2.4 bar, 100% O_2), caffeine, or lidocaine (2.5 bar, 100% O_2).

In conclusion, a single exposure to hyperbaric or hyperoxic conditions does not seem to affect single-dose pharmacokinetics of drugs metabolized and/or eliminated by the kidney (e.g., gentamycin) or by the liver with a capacity-limited clearance (e.g., pentobarbital, theophylline, and caffeine) or with a perfusion-limited clearance (e.g., pethidine, lidocaine; [101]).

HBO therapy is performed in hyperbaric chambers, where this special environment can be achieved. There are chambers available for large animals, too.

Therapeutic Effects of HBO

The typical aim in using HBO is to reverse hypoxia in order to alter ischemic effect or influence vascular reactivity [15]. Postischemic HBO affords clinical and histopathological neuroprotection after experimental cardiac arrest and resuscitation (A/R) and this neuroprotection results from improved cerebral oxygen metabolism after A/R. It was proven by an experiment when anesthetized adult female beagles underwent A/R and randomization to HBO (2.7 ATA for 60 min, 1 h after A/R) or control ($PO_2 = 80\text{--}100$ mm Hg; 1 ATA). Animals underwent neurological deficit scoring (NDS) 23 h after A/R.

Neuronal death (necrotic and apoptotic) in representative animals was determined stereologically in the hippocampus and cerebral neocortex. NDS improved after A/R in HBO animals. Histopathological examination revealed significantly

fewer dying neurons in HBO animals; the magnitude of neuronal injury correlated well with NDS. HBO inhibited neuronal death and improved neurological outcome after A/R. It was also stated that the mechanism of HBO neuroprotection is not due to stimulation of oxidative cerebral energy metabolism [100]. Other typical use of HBO therapy is to reduce edema [84, 85] as hyperoxygenation will cause vasoconstriction, which is considered a side effect of HBO therapy. Although vasoconstriction may be present, there is more oxygen delivered to the tissues. HBO can modulate nitric oxide (NO) production [26, 86, 109]. An increase of nitric oxide leads to vasodilation whereas a decrease of nitric oxide leads to vasoconstriction. Carbon dioxide increases NO production and oxygen decreases NO production by the endothelial cells. HBO modifies growth factors and cytokine effect by regulating their levels and/or receptors [136, 144].

Enhancing wound healing is a main purpose of HBO therapy. Despite the unclear mechanisms involved in the efficacy of HBO therapy in this process it has been proven that there is a significant increase in local wound NO levels after successful HBO therapy. This suggests that this mechanism may be an important factor in promoting enhanced wound healing and wound closure [16]. Vascular endothelial growth factor (VEGF) is important for the growth and survival of endothelial cells, and is found in plasma, serum, and wound exudates. Under normobaric conditions, VEGF is stimulated by hypoxia, lactate, nitric oxide, and nicotinamide adenine dinucleotide (NAD). HBO induces production of VEGF thereby stimulating more rapid development of capillary budding and granulation formation within the wound bed. HBO induces changes in membrane proteins affecting ion exchange and gating mechanisms. HBO also promotes cellular proliferation [38, 52, 83, 109], accelerates collagen deposition, stimulates capillary budding and arborization, and therefore indicates reparative and regenerative tissue mechanisms. In spite of previous reports there are some contradictions, too. In an experiment, on day 0, two 4-cm-diameter circular sections of full-thickness skin were removed from each of two randomly selected limbs of each horse, and two 4-cm-diameter circular skin grafts were harvested from the pectoral region. The horses then received HBO therapy for 1 h daily at 1.84 ATA for 7 days. On day 21, the grafts applied on day 14 were biopsied. Histological examination of biopsy specimens revealed that grafts treated with HBO therapy developed less granulation tissue, edema, and neovascularization, but more inflammation. The superficial portion of the graft was also less viable than the superficial portion of those not treated with HBO therapy. In conclusion, the use of HBO therapy after full-thickness skin grafting of uncompromised fresh and granulating wounds of horses is not indicated [140].

HBO therapy also alleviates osteogenesis. Moreover, in a distraction osteogenesis experiment HBO appeared to accelerate ossification and vascularization of regenerated bone in the distracted area, while applying HBO to tooth movement into a distracted area [53]. HBO therapy accelerates microbial oxidative killing by providing oxygen for the phagocytosing cells and by improving select antibiotic exchange across membranes [88, 91, 92], whereas anoxia decreases the activity of several antibiotics (aminoglycosides, sulfonamides, fluoroquinolone). By raising the pO_2 of ischemic tissue to normoxic levels, it may normalize the activity of these

antimicrobials. In addition, HBO may potentiate the activity of certain antimicrobials by inhibiting their biosynthetic reactions in bacteria. HBO also interferes with bacterial disease propagation by denaturing bacterial toxins and modulates the immune response system. HBO enhances de novo synthesis or activation of oxygen radical scavengers, thereby decreasing ischemia–reperfusion (I–R) injury [123, 142]. This mechanism can be described by the following.

1. HBO therapy increases the amount and activity of the free radical scavenger superoxide dismutase (SOD).
2. Decreased neutrophil adhesion and subsequent release of free radicals is an important early event leading to endothelial damage and microcirculatory failure associated with I–R Injury. HBO reversibly inhibits the $\beta 2$ integrins, therefore inhibiting the neutrophil–endothelial adhesion.

An example of the beneficial effect of HBO therapy is the treatment of necrotizing fasciitis. Compared to national reports of outcomes with “standard” regimens for necrotizing fasciitis, the author’s experience with HBO therapy, adjunctive to comprehensive and aggressive management, demonstrates reduced mortality (34% vs. 11.9%), and morbidity (amputations 50% vs. 0%). The treatments were safe and no delays to surgery or interference with standard therapy could be attributed to HBO therapy [27]. Moreover, in a study of chronic diabetic patients with lower extremity wounds the authors proved the efficacy of HBO therapy. Patients managed in a state-of-the-art wound care center experienced progress toward wound healing, regardless of the treatment modality selected. Those who received HBO as part of their wound care regimen healed faster than those who received standard treatment or growth factor therapy [74].

Complications and Side Effects of HBO Therapy

Although any therapeutic application of hyperbaric oxygenation is intrinsically associated with the potential for producing mild to severe side effects, the appropriate use of hyperoxia is one of the safest therapeutics available to the practitioner [110]. CNS oxygen toxicity can occur at levels of 3 ATA for 1–2 h. Signs in humans include convulsions, nausea, dizziness, muscle twitching, anxiety, and confusion. Pulmonary oxygen toxicity is usually associated with prolonged exposure to HBO. Onset of symptoms has been noted to occur 4–6 h at 2 ATA. Symptoms include dyspnea, shortness of breath, chest tightness, and difficulties inhaling a deep breath. Possible causes for pulmonary toxicity include thickening of the alveolar membrane and pulmonary surfactant changes. Prevention of these side effects includes removal from the oxygen source when first signs occur and no 100% oxygen at pressures greater than 3 ATA. HBO retains the biochemical properties of platelets as proven by *in vitro* studies.

Isolated horse platelets were exposed to 100% oxygen at 2.2 atmospheres, or 100% oxygen under normobaric conditions, or air under normobaric conditions for 90 min. There were no differences in platelet SOD activity among the above-mentioned

conditions, but there was a rise in SOD in all cases after 24 h. However, no catalase (CAT) activity or GSH concentration of platelets changed over time [108]. HBO is frequently used to treat conditions involving some degree of local hypoxia, but can have a direct effect on red blood cell (RBC) deformability. To investigate this, 12 normal dogs received a 10-week “clinical” course of HBO: one 90-min treatment per weekday at 2.4 ATA (243 kPa), 100% O₂. On Mondays and Fridays, a blood sample was drawn. Cells were filtered under a constant of 1.08 kPa through a precalibrated nucleopore hemafil polycarbonate membrane. Filtrate of blood cells was collected for 1 min and weighed, and the RBC “incremental volume” calculated. No significant change was seen in filtration rates, indicating that HBO itself neither improves nor impairs dog RBC deformability. Changes in other commonly measured blood parameters remained within normal values. An acute fluid shift out of RBCs and into plasma was indicated [76].

A study was performed using 1-day to 70-day-old puppies placed in a pressure chamber. The pressure of pure O₂ in the chamber was raised by 5 atmospheres (ATA, 75 psi = 6 ATA) within 10 min. The first biochemical change to take place during HBO was oxidation of mitochondrial NADH. The age of the puppy was found to affect the time to the initiation of seizures. In the puppies under the age of 24 days, the average time was 35.1 ± 5.9 min. In those puppies 24 days old and older, the average time was 5.1 ± 0.8 min. In the younger puppies, there was a later occurrence of blood vessel contractions and a longer lifespan compared to the older puppies. The comparison between the puppies of different ages during exposure to HBO showed differences in the metabolic response, hemodynamic changes, and electrical activity. These differences can partially explain the higher resistance in the younger puppies to HBO [140].

The Use of HBO in Veterinary Medicine

The use of HBO in veterinary medicine is in its infancy. The Hagyard Equine Medical Institute, McGee Medical Center, has currently treated more than 100 patients in their HBO chamber. Patients included pregnant animals as well as neonatal foals with no adverse effects noted. Patients have been pressurized from 2 to 3 ATA ranging from 60 to 90 min at treatment pressure (depth). They have used HBO as adjunctive therapy for:

- Fungal disease (fungal pneumonia)
- Thermal burns, carbon monoxide, smoke inhalation
- Closed head injuries
- Ileus
- CNS edema/perinatal asphyxia
- Peripheral neuropathies
- Sports injuries (exertional rhabdomyolysis)
- Cellulitis, compartment syndrome
- Ischemic injuries (laminitis)

Contraindications for HBO therapy are unknown for horses but may include untreated pneumothorax, high fevers (predisposition to oxygen toxicity), emphysema, and upper airway occlusions [114].

Specific Inflammatory Disorders in Animals

Inflammation in General (Endotoxemia, Systemic Inflammatory Response Syndrome)

Small natural elements such as microbes can cause severe inflammatory processes. “*Et neglecta solent incendia sumere vires*” (Neglected fires are wont to gather strength) [49]. As Horace (Horatius 65–8 BC) mentioned, neglected smaller problems can cause trouble, too. Several antioxidants are available for therapeutic use in acute inflammatory diseases, such as systemic inflammatory response syndrome (SIRS) as caused, for example, by endotoxaemia. They include natural molecules normally present in the body (SOD, alpha-tocopherol, glutathione and its precursors, ascorbic acid, adenosine, lactoferrin, and carotenoids) as well as synthetic antioxidants (such as thiols, ebselen, xanthine oxidase inhibitors, phagocyte function inhibitors, iron ion chelators, and probucol). The therapeutic efficacy of SOD, alpha-tocopherol, and ascorbic acid in the treatment of human disease has generally been unimpressive to date although dietary deficiencies of the last two molecules should certainly be avoided. Xanthine oxidase inhibitors may be of limited relevance as antioxidants for human use. Exciting preliminary results with probucol (anti-atherosclerosis), ebselen (anti-inflammatory), and iron ion chelators (against thalassemia, leukemia, malaria, stroke, traumatic brain injury, and hemorrhagic shock) need to be confirmed by controlled clinical trials. Clinical testing of NAC in HIV-1-positive subjects may also be merited [42].

It was demonstrated that the antioxidant enzyme SOD prevents inflammation and chemotaxis of neutrophils [79]. Burn is a typical damage that causes severe inflammatory and free radical-producing processes. In a study it was reported that SOD and CAT were helpful in ameliorating the damaging effects of burn.

It is known that there is marked volume loss following thermal trauma. Lipxygenase transformation of fatty acids to fatty acid hydroperoxides is a pathway that produces superoxide anion and metabolism upon plasma volume loss. The effects of indomethacin (a cyclo-oxygenase inhibitor), orgotein (SOD-like enzyme), and CAT were studied in anesthetized dogs receiving a 15% total body surface area third-degree flame burn. The results of this study showed that indomethacin did not alter postburn plasma volume loss, orgotein reduced early plasma volume loss but did not reduce continuing loss, and CAT reduced both early and continuing plasma volume loss [46].

Not only antioxidants have anti-inflammatory properties, but several anti-inflammatory agents can also be antioxidant. Among the anti-inflammatory drugs,

aspirin and salicylic acid act as antioxidants, showing a similar, but only modest, magnitude and velocity of superoxide scavenging [120].

Some other drugs, such as oxymetazoline are neither anti-inflammatory, nor antioxidant per se, but inhibit some effects of inflammation and cause decreased oxidative stress. Oxymetazoline, as a nasal decongestant, effectively reduces rhinitis symptoms. It affects arachidonic acid-derived metabolites concerning inflammatory and oxidative stress-dependent reactions. In canine alveolar macrophages, oxymetazoline suppressed pro-inflammatory reactions including 5-lipoxygenase activity, LTB_4 , and respiratory burst and prevented particle-induced oxidative stress, whereas phospholipase A_2 activity and synthesis of immune-modulating PGE_2 and 15-HETE were not affected [8].

In different pathological conditions, such as SIRS, it was demonstrated that much of the cellular injury associated with SIRS is mediated by oxygen or nitrogen free radicals produced by inflammatory cells that overwhelm endogenous antioxidants. Reduced glutathione is a crucial intracellular antioxidant that becomes depleted during SIRS. Regeneration of glutathione can be achieved by acetyl-cysteine, which unlike glutathione itself penetrates cells. In animal models of sepsis and lung injury, acetylcysteine mitigates the cytopathological effects of SIRS. In humans, clinical benefit has been demonstrated in the SIRS of established fulminant hepatic failure. The animal and human studies are sufficiently encouraging to warrant formal trials to test the hypothesis that acetylcysteine therapy has a cytoprotective effect in sepsis [43].

NAC, as mentioned, is a glutathione precursor, and inhibits the *in vivo* effects of endotoxemia in sheep and prevents the most severe effects of endotoxic shock in dogs [7, 115]. In spite of these findings NAC failed to prevent severe effects of endotoxemia, when pigs received continuous intravenous endotoxin for 12 h. Despite the increased glutathione concentration, NAC (150 mg/kg loading dose over 1 h followed by 20 mg/kg bw/h for 11 h) did not improve systemic, pulmonary, and hepatosplanchnic hemodynamics, oxygen exchange, or metabolism. When compared with previous reports in the literature, a different timing of NAC administration and/or an ongoing or even NAC-induced aggravation of oxidative stress may account for this result [132].

Zinc also has a beneficial effect in ameliorating the effects of inflammatory disorders. It has been proposed that metalloprotein zinc mobilization mediated by hypochlorous acid (HOCl) may induce cell injury [31]. Using a dimercaptopropanol-zinc complex it was proven that, once released from thiolate bonds by HOCl, zinc can exert a significant antioxidant effect on both linolenic acid and deoxyribose oxidation induced by iron. In experimental conditions, however, the antagonism toward deoxyribose oxidation is notably less than that toward linolenic acid peroxidation, thus suggesting a more specific inhibitory effect of zinc on iron-mediated oxidant damage when polyunsaturated fatty acids (PUFA) represent the oxidizable substrate. The antioxidant effects of zinc are strictly related to the “free” form; the dimercaptopropanol-zinc complex per se is stimulatory even on biomolecular oxidant damage, apparently as a result of the pro-oxidant interaction of the thiol compound with iron. In light of these results, it may be proposed that the zinc released from

thiolate bonds by HOCl could specifically limit the tissue oxidative burden in pathological conditions involving neutrophil accumulation and activation, such as inflammation and ischemia-reperfusion [67].

There are some novel anti-inflammatory and antioxidant derivatives, such as the sesquiterpenoids. It was reported that the anti-inflammatory activity of avarol and avarone, sesquiterpenoid derivatives from the Mediterranean sponge *Dysidea avara*, potently inhibited carrageenan-induced paw edema as well as ear edema induced by 12-*O*-tetradecanoylphorbol acetate in mice, with effects comparable to those of indomethacin. In stimulated rat peritoneal leukocytes, avarol showed inhibition of LTB₄ and thromboxane B₂ release, respectively, with avarone showing a slightly lower potency. Both marine metabolites failed to show xanthine oxidase inhibitory activity or superoxide scavenging effects but were potent inhibitors of superoxide generation in rat peritoneal leukocytes. Only avarol was able to inhibit human recombinant synovial phospholipase A₂ activity. Avarol and avarone effectively control acute inflammation in experimental models after either oral or topical administration and their anti-inflammatory activity may result from inhibition of eicosanoid release and depression of superoxide generation in leukocytes [30].

Other antioxidants, such as 21-aminosteroids might also be helpful. Effects of the antioxidant, 21-aminosteroid U-74006F (tirilazad mesylate), was demonstrated on the systemic and regional hemodynamics and the oxygen extraction capabilities during endotoxic shock of dogs. Compared with the endotoxin-alone group, the U-74006F-treated dogs maintained higher mean arterial pressure, cardiac index, stroke volume index, and left ventricular stroke work index and lower pulmonary vascular resistance.

Authors also showed a higher fractional blood flow to mesenteric and renal beds [143]. Another radical scavenger, tempol, partially prevented live bacteria from causing key features of hemodynamic and metabolic derangements in porcine hyperdynamic sepsis and beneficially affected surrogate markers of sepsis-induced endothelial and coagulation dysfunction. Sepsis was induced and maintained for 24 h with continuous infusion of live *Pseudomonas aeruginosa*.

Tempol significantly attenuated reduction in mean arterial pressure. Despite comparable mesenteric macrocirculation, tempol attenuated the otherwise progressive deterioration in ileal mucosal microcirculation and prevented mucosal acidosis. Tempol also reduced nitrosative stress without significant effect on the gradual increase in plasma 8-isoprostanes, meta-stable end-products of lipid peroxidation (LPO). Tempol attenuated sepsis-induced endothelial (von Willebrand factor) and hemostatic (thrombin-antithrombin complexes, plasminogen activator inhibitor-type 1) dysfunction [77].

Nitric oxide plays an important role in systemic inflammatory responses. This was proven by the experiment in which ewes were chronically instrumented methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis. This group developed impaired gas exchange and significantly increased lung lymph flow, permeability index, and bloodless wet-to-dry weight ratio (W/D ratio). The plasma nitrate/nitrite (NO_x) levels, lung inducible nitric oxide synthases (iNOS) and endothelial nitric oxide synthases (eNOS), VEGF protein expressions, and poly-(ADP)-ribose (PAR) were significantly increased by the MRSA challenge [57].

Nonselective NOS inhibition in sepsis models reversed sepsis-induced derangements in hemodynamic status, but was associated with side effects such as pulmonary vasoconstriction and decreases in global oxygen delivery. Results from studies on specific inhibition of iNOS (NOS-2) and neuronal NOS (nNOS, NOS-1) in sepsis models remain inconclusive, but suggest that both isoenzymes are involved in the pathophysiological processes [66].

Different doses of L-arginine, which is a NO precursor, similarly increased mortality, and worsened shock (for reduced mean arterial pressure). These effects were associated with significant increases in plasma arginine and ornithine. In addition, serum nitrate/nitrite, liver enzymes, and blood urea nitrogen/creatinine ratios rose, whereas arterial pH and bicarbonate levels fell. NAC did not significantly decrease any of the harmful effects of L-arginine. Thus, parenteral L-arginine monotherapy was markedly harmful in animals with septic shock [58].

It has been found that lysozyme (Lzm-S), released from leukocytes, contributed to the myocardial depression that develops in a canine model of septic shock. Lzm-S binds to the endocardial endothelium, resulting in the production of nitric oxide, which, in turn, activates the myocardial soluble guanylate cyclase (sGC) pathway. In a phenylephrine-contracted canine carotid artery ring preparation, the authors found that canine Lzm-S, at concentrations similar to those found in sepsis, produced vasorelaxation. This decrease in force could not be prevented by inhibitors of NO synthase, prostaglandin synthesis, or potassium channel inhibitors and was not dependent on the presence of the vascular endothelium. However, inhibitors of the sGC pathway prevented the vasodilatory activity of Lzm-S. *Aspergillus niger* CAT, which breaks down H_2O_2 , as well as other hydroxyl radical scavengers, such as hydroquinone and mannitol, prevented the effect of Lzm-S [81].

Pulmonary and Other Airway Inflammatory Diseases

Pulmonary diseases are typical life-threatening disorders. The well-known Latin saying is “*Dum spiro, spero* (while I breathe, I have hope, or in other words: I have hope while I am alive).” It is necessary to protect pulmonary tissue from the damaging effects of free radicals and inflammatory processes, as a slight problem can cause a severe decrease in oxygenation.

The mechanism of recurrent airway obstruction (RAO) in horses was investigated by measuring the membrane domain structure and oxy-redox activity in phagocytes isolated from bronchoalveolar lavage fluid (BAL) and from the blood of healthy and RAO horses by electron paramagnetic resonance (EPR). It was also found that the phagocytes were affected by oxidative stress in RAO horses proven by the altered activity of intracellular antioxidant enzymes CAT, GPx, and SOD measured in phagocytes. In comparison with polymorphonuclear leukocytes (phagocytes) from the blood of healthy horses the reduction mechanisms in BAL were faster and coincided with the merging of disordered membrane domains, whereas in horses with RAO the reduction and membrane domain structure remained unchanged. The merging of lipid domains observed in phagocytes from

BAL of healthy horses could promote cluster formation of membrane proteins or ligands, which could trigger the activation process in phagocytes of healthy horses and consequently the physiological response that probably did not happen in phagocytes of RAO horses [65].

Antioxidant supplementation is therefore warranted in horses with RAO. Antioxidant supplement tested modulated oxidant/antioxidant balance and airway inflammation of heaves-affected horses. The antioxidant treatment (vitamins E and C and selenium) significantly improved exercise tolerance and significantly reduced endoscopic inflammatory score. Plasma uric acid concentrations were significantly reduced, suggesting downregulation of the xanthine-dehydrogenase and xanthine-oxylase pathway. RBC hemolysate glutathione content showed an insignificant trend to increase, whereas plasma 8-epi-PGF_{2alpha} remained unchanged. Pulmonary markers and BAL cytology were not significantly affected by antioxidant supplementation [62].

The antioxidant ascorbic acid supplementation does not alter basic antioxidant levels apart from ascorbic acid itself. The authors reported that the concentration of lung lining fluid ascorbic acid is increased following ascorbic acid oral supplementation (20 mg/kg body weight) in an ascorbate-synthesizing species. Two weeks' supplementation with ascorbyl palmitate increased mean plasma ascorbic acid concentrations compared to control. The concentration of ascorbic acid in BAL increased in five out of six ponies following supplementation with either ascorbyl palmitate compared to control. Neither supplement altered the concentration of glutathione, uric acid, or alpha-tocopherol in plasma or BAL [24].

Apart from the well-known antioxidants, it was demonstrated that another antioxidant, taurine, via *N*-chlorotaurine formation may protect the lung from oxidant-induced injury by inhibiting production of nitrite and the release of TNF-alpha which are both known to be directly linked to tissue injury [106].

Inflammatory Kidney Diseases

Our ancestors knew that urine was a good indicator of kidney disease. *A fonte puro pura defluit aqua* (Clear water flows from a clear spring). The kidney has to work properly. If it is healthy, urine looks healthy, too. Inflammation is a typical cause of kidney failure. In a study authors examined the oxidative stress markers in azotemic dogs. They found that dogs with renal azotaemia had higher intraerythrocytic sodium content. The RBC CAT activity and glutathione content and plasma malondialdehyde (MDA) level were unaltered whereas the urinary malondialdehyde-creatinine ratio (U-MDA/Cr) increased. The U-MDA/Cr was correlated with plasma creatinine concentration, urinary protein-creatinine ratio, and fractional excretion of sodium [17].

The antioxidant vitamin E ameliorates the effects of glomerular disease. Authors reported that IgA nephropathy is one of the most common forms of glomerular disease. Nearly 25% of affected patients progress to end-stage renal disease

over a 20–25-year follow-up period. IgA-containing immune complexes stimulate oxygen-free radical production by mesangial cells *in vitro*. The excessive oxidant stress may mediate glomerular injury in this disorder. IgA nephropathy with mild kidney inflammation was induced in Lewis rats by oral immunization with 0.1% bovine gamma-globulin (BGG)-containing drinking water. Vitamin E-treated rats gained more live weight and had a lower incidence of hematuria and proteinuria, and reduced renal plasma flow was restored to normal value, compared to untreated rats with IgA nephropathy. Glomerular hypertrophy occurred in animals with IgA nephropathy, but less so in those receiving vitamin E supplementation. Renal cortical MDA content was reduced in rats fed the vitamin E-enriched diet. Finally, renal transforming growth factor-beta 1 gene expression was reduced by 34% in rats with IgA nephropathy receiving vitamin E treatment. It can be concluded that experimental IgA nephropathy is associated with increased renal oxidant injury. Dietary treatment with the antioxidant vitamin E attenuated renal functional and structural changes in experimental glomerulopathy [124].

A potential treatment option is providing a very low protein diet supplemented with amino and keto acids and vitamins A, C, and E (VLPD) to patients with chronic renal failure (CRF). It was demonstrated that VLPD has a protective role against LPO of erythrocytes in patients with CRF. Peuchant [94] have evaluated parameters indicative of LPO of RBC at baseline in patients with CRF compared to controls, and the effects of a very low protein diet supplemented with amino and keto acids and vitamins A, C, and E over a 6-month period. The presence of peroxidative damage in CRF patients before the administration of VLPD was demonstrated by elevated levels of free MDA and decreased levels of PUFA, as compared to controls. Similarly, RBC vitamin E content was decreased whereas enzymatic activities were unaltered. Peuchant suggested that VLPD-reduced erythrocyte LPO was proven by (a) decreased levels of free and total RBC MDA, (b) increased levels of PUFA, and (c) increased levels of vitamins A and E as compared to prediet results. However, antioxidant enzyme activities were not modified [94].

Moreover, 21-aminosteroid (21-AS) and mannitol have synergistic effects in the case of kidney damage. Salahudeen [102] reported that, employing Raman spectroscopy, they confirmed *in vitro* the ability of 21-AS to inhibit iron-induced fatty acid peroxidation. The 21-AS was then administered to rats developing renal failure from glycerol-induced rhabdomyolysis. Although 21-AS inhibited rhabdomyolysis-induced plasma and renal LPO, renal protection was incomplete. Applying fluid-alkaline-mannitol (FAM) diuresis to inhibit cast formation afforded better renal protection. However, when these therapies were combined to inhibit both LPO and cast formation, there was synergistic renal functional protection. This was accompanied by a maximum inhibition of renal and plasma LPO, as well as renal tubular necrosis and cast formation. Compared to combination therapy, FAM therapy alone, despite identical volume, was accompanied by a higher tubular necrosis and cast formation [102].

Kidney transplantation is a great challenge in humans. The canine autotransplantation method is a good model to evaluate the technical problems and ischemia–reperfusion (I/R) injury in this intervention. Antioxidant supplementation seems

to be effective in alleviating the reperfusion injury caused by oxidative stress. In a study authors found that antioxidant enzyme activity in blood plasma was significantly lower in the control group than in the ascorbic acid supplemented (cold normal saline and ascorbic acid in a dose of 100 mg/kg was perfused followed by autotransplantation) treatment group. The histopathology findings revealed the treatment group to have less damage than the control group. The results of this study suggest that ascorbic acid alone might play a role in attenuating I/R injury and assist in the recovery of the renal function in a renal transplantation model [69].

Gingivitis

To keep teeth healthy could be important in the past, as they were considered as weapons. As Lucretius (99–55 BC) said: “Arma antiqua manus ungues dentesque fuerunt (Ancient weapons were hands, nails, and teeth)” [73]. Inflammatory processes of the oral region such as gingiva are common in humans, and many animal models are used to get adequate information about the development of the disorders and possible treatment options. This disease group can cause severe harm in canine patients, too. Antioxidants provide a hopeful alternative way of treatment.

Cu/Zn-SOD has moderate anti-inflammatory activity which could be enlarged by encapsulation into liposomes. The greater efficiency of liposomal SOD compared to the free enzyme is explained by an increased fixation to cell walls as well as with improved tissue penetration. It was shown that liposome-encapsulated SOD penetrates into the cell probably by endocytosis [126]. The phagocytes are present in abundance in inflamed periodontal tissues [9]. The hypothesis that highly reactive radicals may be responsible for the initial degradation of extracellular matrix components seen in periodontal disease is in agreement with Misaki et al. [82] who showed pronounced better healing of gingivae wounds in rats after i.v. application of SOD [82]. SOD also prevents amplification and interrupts cascade processes of free radical formation, that is, single superoxide molecule interaction with lipids, H_2O_2 , flavins to other radicals [80]. Moreover, production of free radicals from freshly cancellous bone specimens was also detected [71] and bone resorption was prevented by application of SOD [98]. Free radical processes are one of the mechanisms by which bone is destroyed under inflammatory circumstances. Drugs that inhibit free radical production or scavenge those radicals may be useful therapeutic agents for local bone destruction [35]. In spite of beneficial effects of this kind of supportive periodontal therapy, we must also be aware that inappropriate concentration of SOD might lead to tissue damage by excessive production of H_2O_2 [75]. However, high production of H_2O_2 might be also beneficial due to antibacterial effect on periodontal pathogens as indicated by Hillman and Socransky [45]. Replacement therapy may also find a practical application in the prevention and cure of certain periodontal diseases. Hydrogen peroxide-producing streptococci are invariably found in plaque taken from healthy gingiva; they are rarely found in

samples from active disease sites of patients with juvenile or refractory periodontitis. Naturally occurring oral bacteria are promising effector strains for the replacement therapy of dental infectious diseases [45].

It was proven that scaling and root planing with subgingival application of liposome-encapsulated SOD suppresses periodontal inflammation and stimulates periodontal healing and alveolar bone apposition on experimentally induced periodontitis in beagle dogs. Further studies are in progress to evaluate the optimal concentration of SOD, CAT, or a combination of both enzymes for suppression of periodontal inflammation [93].

Nitric oxide is a free radical produced in host tissues by constitutive and inducible forms of the enzyme nitric oxide synthase. Nitric oxide plays physiological roles, but it is also involved in the pathophysiology of several inflammatory conditions, such as gingivitis. Local increases in iNOS and reactive nitrogen products have also been demonstrated in humans and animals with periodontal disease. A placebo-controlled preclinical investigation examined the effect of two mercapto-alkylguanidines, mercapto-ethylguanidine (MEG) and guanidine-ethyldisulfide (GED), which are iNOS inhibitors and reactive nitrogen radical scavenging compounds, on the development of experimental gingivitis in beagle dogs. Experimental gingivitis was then induced, with cessation of plaque control and institution of a soft diet over 8 weeks. Beagles randomly received 0.3% MEG, 0.3% GED, or placebo (vehicle) gels, topically applied twice daily to premolar teeth. At weeks 2, 3, 4, and 8, gingival index scores were significantly lower for MEG and GED groups compared to the placebo group. In addition, MEG and GED gels significantly reduced gingival bleeding responses by 8 weeks. The data from this preclinical study indicate that mercapto-alkylguanidines, topically administered, may significantly reduce experimental gingivitis in the beagles [89].

Uveitis and Canine Cataract

We know that “*In oculis animus habitat* (The soul dwells in the eyes),” therefore much attention must be paid to the inflammatory processes of the eye. It can be important to use antioxidants in ocular disorders, too. The experimental autoimmune disease elicited by a large dose of retinal S antigen in guinea pigs is characterized by massive necrotizing uveitis and retinitis. It was proven that SOD prevents S-antigen-induced experimental autoimmune uveoretinitis (EAU) in guinea pigs, and bovine serum albumin-induced passive Arthus type uveitis in rabbits. These results suggest that superoxide may play a role in causing tissue damage in animal models of ocular inflammation and possibly in Behcet disease [139].

Similarly to the previous experiment, S-antigen-induced EAU in guinea pigs treated with the antioxidants SOD, CAT, and sodium benzoate resulted in marked reduction of uveal inflammation. The attenuated inflammation was characterized by a relatively well-preserved retina and retinal pigment epithelium along with a reduction of subretinal exudate and vitreous inflammation [97].

Not only antioxidant enzymes, but also other antioxidant substances, such as deferoxamine can be used in treating uveitis. Because photoreceptors contain a high proportion of PUFA, deferoxamine, in turn, will act to ameliorate the experimental autoimmune uveitis-mediated retinal degeneration. Treatment of experimental uveitis in Lewis rats with an iron chelator, deferoxamine mesylate, resulted in a marked reduction in choroidal inflammation and suppression of retinal damage [96]. Moreover, in vitro addition of 10 mM deferoxamine, the free radical generation of inflamed retina was suppressed by nearly 40% [138]. Other antioxidant substances were also helpful in uveitis. The lipoxygenase inhibitors phenidone and nordihydroguaiaretic acid, and dimethyl sulfoxide decreased fibrin production at 0.5 and 1 h after induction of uveitis. Phenidone and nordihydroguaiaretic acid also inhibited the initial increase in intraocular pressure early in the course of inflammation [25].

Babizhayev [145], Williams and Munday [137] have proven that *N*-acetyl carnosine can treat immature lens opacities and nuclear sclerosis in dogs. The dogs were treated three times daily with topical 2% *N*-acetyl carnosine in a buffered vehicle containing glutathione, cysteine, ascorbate, L-taurine, and riboflavin (Ocluvet®, Practivet, Phoenix, AZ, USA). The examination was performed prior to treatment and at 2, 4, and 8 weeks during treatment, by direct and indirect ophthalmoscopy and slit-lamp biomicroscopy after pharmacological pupil dilation. This study demonstrated some marginal reduction in lens opacification of canine cataract. Lens opacification was improved with treatment in eyes with immature cataract or nuclear sclerosis whereas in eyes with mature cataract or cataract with associated intraocular inflammatory pathology less reduction was seen [137].

Dermatitis

“Floreat curator cutis (May the manager of the skin prosper),” said old Latin. To treat skin problems is essential. There are many antioxidants used in various human and animal inflammatory skin disease, such as silibinin, silymarine, and other flavonoids, furfuryl palmitate, pentoxifylline, melatonin, vitamin E, retinol, selenium salts, NAC, Ginkgo biloba extract, topically applied SOD, beta-carotene, bucillamine, and so on. Still there are open questions and quite a few basic contradictions even in connection with the application of the most commonly used lipophilic antioxidant vitamin E in skin disorders. It has been used for more than 50 years in clinical and experimental dermatology. Although a large number of case reports were published, there is still a lack of controlled clinical studies providing a rationale for clinical indications and dosage. In contrast, advances in basic research on the physiology, mechanism of action, penetration, bioconversion, and photoprotection of vitamin E in human skin have led to the development of numerous new formulations for use in cosmetics and skin care products. Although its current use is largely limited to cosmetics, controlled clinical studies for indications such as atopic dermatitis or prevention of photocarcinogenesis are needed to evaluate the clinical benefit of vitamin E [122].

In a study of feline perforating dermatitis authors applied methyl-prednisolone acetate (20 mg/cat im) and vitamin C (100 mg/kg twice a day for 2 months). Vitamin C administration failed to resolve the disease. In two cases, methyl-prednisolone acetate was used to manage relapsing episodes and vitamin C helped to reduce glucocorticoid requirements [2].

Osteoarthritis, Synovitis

Painless bones are essential for living a comfortable life. Ovid (43 BCE–18 CE) needed to keep his bones comfortable in his grave, too. “*Nasonis molliter ossa cubent* (May the bones of Naso lie gently)” [87]. The development of osteoarthritis is highly dependent on the antioxidant system. In addition to matrix metalloproteinases, ROS are the main causative agents of cartilage degradation. To prevent ROS toxicity, chondrocytes possess a well-coordinated enzymatic antioxidant system formed principally by SODs, CAT, and glutathione peroxidase (GPX). Mathy-Hartert [78] proved the dysregulation of the antioxidant enzymatic system due to inflammatory mediators. Bovine chondrocytes were cultured in monolayer in the absence or presence of IL-1beta or IL-6. To study the signal transduction pathway, inhibitors of mitogen-activated protein kinases (MAPK; PD98059, SB203580, and SP600125) and nuclear factor (NF)-kappaB inhibitors (BAY11-7082 and MG132) were used. Mn-SOD and GPX activities were dose- and time-dependently increased by IL-1beta. In parallel, IL-1beta markedly enhanced Mn-SOD and GPX gene expressions, but decreased Cu/Zn SOD, EC-SOD (which is a copper-containing enzyme also known as SOD3; it has the major role in vessel walls; Itoh 2009 [55]) and CAT gene expressions. Induction of SOD enzymatic activity and Mn-SOD mRNA expression were inhibited by NF-kappaB inhibitors but not by MAPK inhibitors. IL-1beta, and to a lesser extent IL-6, dysregulates enzymatic antioxidant defenses in chondrocytes. These changes could lead to a transient accumulation of H₂O₂ in mitochondria, and consequently may cause mitochondrial damage. These changes contribute to an explanation of the mitochondrial dysfunction observed in osteoarthritis chondrocytes [78]. Therefore the use of antioxidants to treat osteoarthritis might be the crucial point in treatment options.

There are hundreds of plants yielding drugs with antioxidant properties used to treat arthritis or osteoarthritis. Until now, little information has been available on the antioxidative status of chondrocytes. Nevertheless, most of the literature suggests that this antioxidant is good and that an antioxidant is even more beneficial in treatment of this disease group. For instance, in vitro experiments in guinea pigs in which a Glynn–Dumonde synovitis was induced with BGG suggest that desferrioxamine inhibits iron-catalyzed LPO when it is poorly saturated with iron, but loses this effect when it is iron saturated [11]. Moreover, it was also stated that hydroxyl radical scavengers can be beneficially used in arthritis. Santos and Tipping [104] reported that the contribution of ROS, in particular hydroxyl radical (OH⁻), to joint inflammation was examined in rats developing adjuvant arthritis

(AA) by treatment with ROS scavengers dimethylthiourea (DMTU) and DMSO. Both DMTU and DMSO significantly reduced the clinical evidence of arthritis; synovial fluid cell accumulation was also significantly reduced compared with disease control [104].

It was also reported that many trials are known to treat arthritis by various antioxidant plant substances. Numerous agents derived from plants can suppress these cell signaling intermediates, including curcumin (from turmeric), resveratrol (red grapes, cranberries, and peanuts), tea polyphenols, genistein (soy), quercetin (onions), silymarin (artichoke), guggulsterone (guggul), boswellic acid (salai guggul), and withanolides (ashwagandha). Indeed, several preclinical and clinical studies suggest that these agents have potential for arthritis treatment. Although gold compounds are no longer employed for the treatment of arthritis, the large numbers of inexpensive natural products that can modulate inflammatory responses, but lack side effects, constitute “goldmines” for arthritis treatment [60]. As one of the most important and useful antioxidants, SOD seems to be effective in treating arthritis in various clinical trials, but the manner of application is problematic. The efficacy of SOD decreases a lot until is penetrating to the site where it is really needed. Therefore liposome-encapsulated SOD is applied and seems to be beneficial, but its activity is still not enough. A new way is the application of acylated superoxide dismutase (Ac-SOD) enzymosome in the liposomal enzymatic system. In this case Ac-SOD is inserted in the lipid bilayer of liposomes, unlike when SOD is located in the aqueous compartment of liposomes. Cruz [146], Gaspar (2006) have found that Ac-SOD enzymosomes are nanocarriers combining the advantages of expressing enzymatic activity in intact form and thus being able to exert a therapeutic effect even before liposome disruption, as well as acting as a sustained release of the enzyme [37].

Despite the many good examples there are numerous contradictory findings known in connection with the efficacy of antioxidant treatment of arthritis. The modification of the antioxidant defense system in this disease group remains unknown. Some antioxidant supplements or drugs with antioxidant properties have been developed to reinforce the cellular antioxidant status. However, until now, there has been no consistent evidence that additional antioxidant supply is efficient to relieve arthritis symptoms or to prevent structural changes in arthritis cartilage [44]. Similarly to the aforementioned skin problems, it was found that clinical trials testing the efficacy of vitamin E in the treatment of osteoarthritis and inflammatory arthritis have been methodologically weak and have produced contradictory findings. There is presently no convincing evidence that melatonin, Amazonian vine, *Withania somnifera* root powder, bucillamine, SOD, glucosamine, chondroitin sulfate, avocado-soybean unsaponifiables, selenium, vitamin A, vitamin C, the combination of selenium compounds, and the like are effective in the treatment of any type of arthritis [18, 33]. Most of these review articles highlight the need for additional randomized, placebo-controlled trials to further define the utility of nutraceuticals and any drug with antioxidant property in arthritis treatment.

The development of osteoarthritic structural changes in the anterior cruciate ligament was examined in a dog model. It was induced by anterior cruciate ligament transection of the right knee in dogs. The dogs were treated with avocado-soybean

unsaponifiables (10 mg/kg per day). The treatment reduced the loss of subchondral bone volume and calcified cartilage thickness as compared to placebo-treated dogs. Immunohistochemical analysis of cartilage revealed that avocado–soybean unsaponifiables significantly reduced the level of inducible nitric oxide synthase and matrix metalloproteinase- (MMP-)13 in cartilage. The beneficial effect of the treatment was suggested as a consequence of the inhibition of inducible nitric oxide synthase and MMP-13, which are key mediators of the structural changes that take place in osteoarthritis [14].

Pancreatitis

Pancreatitis is a life-threatening disease. This section gives some points to overcome this disorder, according to the theory of Cicero: “*Conqueri fortunam adversam, non lamentari decet* (You should fight against misfortune instead of mourning about it;” Marcus Tullius Cicero 106–43 BC; [131]). Antioxidants can also be used in the treatment of acute pancreatitis. Similarly to other diseases, a wide scale of antioxidants was examined in this disease. Here we focus on some important and interesting studies. The efficacy of antioxidant enzyme treatment was evaluated. Schoenberg et al. [105] reported that treatment with SOD (100,000 U/kg/h) and CAT (400,000 U/kg/h) prevented LPO and reduced zymogen degranulation and tissue necrosis, but tissue edema and inflammatory response were not affected in both models (cerulein, sodium taurocholate) of acute pancreatitis [105]. Other drugs with atypical antioxidant properties were beneficial in preventing inflammatory and free radical producing processes. BN 52021-platelet activating factor (PAF) receptor antagonist had a beneficial effect against cerulein-induced acute pancreatitis in rats depending on the prevention of inflammatory cell activation and subsequent generation of oxygen radicals within pancreatic tissue.

There was significant reduction of pancreas edema, diminution of hyperamylasemia, lack of SOD activity depletion, and inhibition of LPO in pancreatic tissue. These changes were accompanied by significant reduction of acinar cell vacuolization and remarkable inhibition of infiltration with inflammatory cells in the interacinar space [23]. The xanthine oxidase inhibitor allopurinol was also examined. It was found that addition of allopurinol to the treatment protocol in acute pancreatitis might improve the pathological score, bacterial translocation, and oxidative stress parameters due to decreasing ROS formation caused by the inflammatory process of the pancreas as there can be a continuous hypoxia reperfusion injury in this disease [54]. Efficacy of other antioxidants, such as resveratrol, melatonin, and pentoxifylline was also examined in acute pancreatitis. Resveratrol seemed to ameliorate the severe effects of this disease. Szabolcs [119] suggested that the beneficial effects of resveratrol on acute pancreatitis seem to be mediated by the antioxidant effect of resveratrol or by an NF-kappa-B-independent anti-inflammatory mechanism. In connection with melatonin, Szabolcs [119] suggested that it is an antioxidant able to counteract some of the L-arginine-induced

changes during acute pancreatitis, and may therefore be helpful in the supportive therapy of patients with acute necrotizing pancreatitis. Pentoxifylline was reported as a methylxanthine derivative with rheological and marked anti-inflammatory properties. It inhibits the production of proinflammatory cytokines. Gomez-Cambronero [39] found that using pentoxifylline attenuated inflammatory responses within the pancreas in acute pancreatitis.

In spite of the wide-scale trial for commonly used antioxidants such as selenium, NAC, and vitamin C in the treatment of acute pancreatitis (and there are many studies that report beneficial effects of these compounds), Siriwardena [113] in a study provide no evidence to justify continued use of these drugs in severe acute pancreatitis. These authors also point out the harmful side effects of these derivatives [113].

Chronic pancreatitis was beneficially treated by a mixture of antioxidants, including selenium, beta-carotene, L-methionine, and vitamins C and E. Treatment with these compounds was associated with significant improvements in quality of life in terms of pain, physical and social functioning, and general health perception. Kirk [61] concluded that treatment with antioxidants may improve quality of life and reduce pain in patients suffering from chronic pancreatitis [61].

Hepatitis

There are various drugs used in liver diseases: more advice, more success. Nevertheless, we have to be aware that “*Facile omnes, cum valemus, recta consilia aegrotis damus* (We all find it easy to give the right advice to the sick when we are well;” Marcus Terentius Varro (116–27 BC) [121]. It was stated that in copper toxicosis (CT) of Bedlington terriers, non-copper-associated chronic extrahepatic cholestasis (EC), or chronic hepatitis (CH), the dogs have reduced protection against oxidative stress, opening a rationale to use antioxidants as possible therapy [117]. The treatment of idiopathic chronic hepatitis consists of controlling inflammation (prednisone, azathioprine), reversing fibrosis (colchicine), and protecting against oxidant damage (vitamin E, ursodeoxycholic acid, S-adenosylmethionine) (Honeckman 2003) [148]. The following concerning the use of antioxidants in the case of hepatopathies is based upon Honeckman’s (2003) article.

Ursodeoxycholic acid is a hydrophilic bile acid with anti-inflammatory, immunomodulating, and choleretic properties. It displaces hydrophobic bile acids that can cause oxidative injury to hepatocytes. Ursodeoxycholic acid may have direct antioxidant effects by increasing glutathione and metallothionein [128]. Ursodeoxycholic acid may also decrease collagen formation [48]. It is useful in humans with primary biliary cirrhosis [111].

Zinc is not only useful for copper-associated hepatopathy but may also be helpful in other forms of chronic hepatitis in dogs because of its antioxidant and antifibrotic effects [70].

Vitamin E is an antioxidant that is recommended at a dose of 50–600 IU per day [128]. Oxidant injury to hepatic mitochondria has been reported in Bedlington terriers with copper storage hepatopathy [116]. There is in vitro evidence suggesting that vitamin E may be useful in preventing oxidative damage to hepatocytes exposed to copper or hydrophobic bile acids [129]. In human studies, vitamin E was helpful in treating patients with chronic hepatitis B [4]. Although there are no controlled studies of its use in canine chronic hepatitis, the use of vitamin E seems reasonable based on experimental studies. Because absorption of fat soluble vitamins may be reduced in cholestatic liver disease, a water-soluble form may be preferred [127].

S-adenosylmethionine is a nutraceutical that has recently been marketed for use in dogs with liver problems. It has anti-inflammatory and antioxidant effects, and also plays a role in cellular replication and protein synthesis [128]. It has been useful for the treatment of acetaminophen toxicity [135], but there are no controlled studies of its use in canine chronic hepatitis.

Silymarin, an antioxidant extracted from milk thistle, has also been recommended for chronic hepatitis [127]. Although silibinin (the main isomer in silymarin) has been proven to be useful for treating amanita mushroom toxicity in dogs and humans [134], there are currently no controlled studies on its use in canine chronic hepatitis. Most studies of milk thistle in humans have shown little or no improvement in biochemical markers, histology of liver biopsies, or survival [56].

Colitis and Giardiasis

Improper eating often comprises the origin of intestinal disease. Therefore, the motto of this section is “*Edas ut vivas, ut edas, noli vivere* (Eat in order to live, and do not live for eating;” Caecilius Balbus 1 BC). There have been numerous experiments done to prove the efficacy of antioxidants in intestinal diseases, too. In a study the effects of gastrointestinal mucosal injury were examined, which was induced by exposing gastric mucosa with bile and a luminal pH of 1 in cats; moreover live *Escherichia coli* was infused i.v. Although hemodynamic responses (mean arterial pressure and cardiac output) were significantly improved in methylprednisolone-pretreated cats, misoprostol/SOD/CAT administered with a nasogastric tube reduced late hypotension. Pulmonary arterial pressure rose to approximately 200% of basal in both methylprednisolone and misoprostol/SOD/CAT administration [5].

It was proven that 5-aminosalicylic acid-containing drugs but, more effectively, specific scavengers, have been found to reduce the intestinal inflammatory process. It is beneficial to use new anti-inflammatory drugs for inflammatory bowel disease specifically designed to scavenge toxic oxygen metabolites [133].

Keshavarzian [59] performed a wide-scale study in connection with the efficacy of different drugs of the antioxidant effect in experimental colitis on rats by acetic acid administration at 2.5%, which produced moderate inflammation. They found that specific superoxide anion scavenger methoxypolyethylene glycol-SOD, and reactive oxygen metabolite scavenger, sulfasalazine, significantly decreased the severity of

inflammation. The xanthine oxidase inhibitors, tungsten and pterin-aldehyde, failed to improve inflammation but another xanthine oxidase inhibitor, allopurinol, a compound with known superoxide anion scavenging effect, did limit the inflammation. Inhibition of hydroxyl radical production by deferoxamine or lowering hydroxyl radical values by a scavenger, dimethyl-sulfoxide, did not affect the severity of inflammation. According to the authors, these data suggest that (1) reactive oxygen metabolites play an important role in experimental colitis, (2) the xanthine oxidase pathway is not a major source of reactive oxygen metabolites in colitis, and (3) tissue injury in experimental colitis is not caused by generation of hydroxyl radicals [59].

Other experiments also prove the benefit of using antioxidants in the early stage of induced colitis in rats. Antioxidant enzymes (such as SOD, GPX) and an antioxidant, alpha-tocopherol, were significantly decreased with the severity of colonic damage. Mn-SOD at a dose of 50,000 U/kg attenuated this colitis when preadministered subcutaneously 1 h before the induction of colitis [141].

Gross [40] used the aminosalicylates in the treatment of inflammatory bowel disease. They found that this compound ameliorated the effects of enteritis. They stated that as aminosalicylates are potent antioxidants, this fact underscores the importance of reactive oxygen metabolites in this disease [40].

Sener [107] performed a really contemporary examination in connection with erdosteine, which is a sulfhydryl-containing antioxidant. The treatment by this compound reversed increases in the colonic luminol and lucigenin chemiluminescence values, macroscopic and microscopic damage scores, MDA and collagen levels, myeloperoxidase activity and DNA fragmentation, decrease in tissue glutathione level, elevated serum cytokines and lactate dehydrogenase activity, and histopathological alterations induced by trinitrobenzene sulphonic acid (TNBS) in Sprague–Dawley rats. The authors suggest that erdosteine protects the colonic tissue via its radical scavenging and antioxidant activities [107].

The antioxidant silymarin can be used beneficially together with traditional treatment. Silymarin, in supplement with antiprotozoal drugs (metronidazole), can beneficially influence the therapy of canine giardiasis. Ten days post-treatment the efficacy of metronidazole plus silymarin (91%) was significantly different in comparison with that of metronidazole (75%). Signs of side effects and decreased body weight were not observed in silymarin plus metronidazole-treated dogs. Poor appetite and intermittent vomiting signs and decrease in body weight were observed in two dogs of the metronidazole-treated group. Two weeks after metronidazole treatment, serum concentration of GOT, GPT, and NH₃ were significantly increased in comparison with those treated with silymarin [21].

Encephalopathy, Neuritis, and Spinal Cord Injury

The central nervous system can also suffer from inflammatory processes. “*Ferunt summos fulmina montes* (Lightning strikes the highest mountain tops;” Horace 65–8 BC) [50]. The iron chelator deferoxamine can be used in treating neuritis. It has been found that conjugated deferoxamine reduces disruption of the blood–brain barrier

and the OH^- radical generated from perivascular H_2O_2 may possibly play a role in alterations of vascular permeability in experimental optic neuritis [41].

Some authors who examined neonates with hypoxic ischemic encephalopathy used a nonantioxidant compound phenobarbital in the therapy, but they found a decrease in LPO products (Gathwala [147], Singh [112]). Singh [112] suggested that phenobarbital in the dose of 20 mg/kg i.v. given within 6 h of life in term and near-term neonates with hypoxic ischemic encephalopathy, was associated with a decrease in lipid peroxides, antioxidant enzymes, and antioxidant vitamins. They demonstrated that there was a trend toward lower levels of cerebrospinal fluid (CSF), MDA content, and activities of SOD and GPx and blood vitamin content of A and E in babies with normal outcome as compared to babies with adverse outcome (death or neurologically abnormal at discharge). Moreover, CSF levels of MDA and activities of SOD and GPx were significantly lower in the group receiving phenobarbital [112].

A new way to treat neuritis is the antioxidant gene therapy which was tested in mice with experimental autoimmune encephalomyelitis (EAE), a strategy designed to treat patients at risk for axonal degeneration and persistent visual loss from optic neuritis and multiple sclerosis. Qi [95] cloned the human extracellular superoxide dismutase (EC-SOD) or CAT gene into recombinant adeno-associated virus (AAV). Animals were sensitized for EAE, followed by serial contrast-enhanced MRI for 6 months, and then were euthanized. The effects of ECSOD and CAT modulation on the EAE optic nerve were gauged by computerized analysis of optic nerve volume, myelin fiber area, axonal cell loss, and retinal ganglion cell (RGC) loss. One month after intraocular injections, transgene expression increased 4-fold for AAV-ECSOD and 3.3-fold for AAV-CAT. Six months after intraocular injections and EAE sensitization, combination therapy with ECSOD and CAT decreased RGC loss by 29%, optic nerve demyelination by 36%, axonal loss by 44%, and cellular infiltration by 34% compared with the contralateral control eyes inoculated with AAV-GFP. It was concluded that viral-mediated delivery of antioxidant genes provides long-lasting suppression against neuronal and axonal loss associated with permanent visual disability in patients with optic neuritis and multiple sclerosis [95].

In spinal cord traumas antioxidants can be beneficially used, but still there are some contradictory findings in connection with their routine application. Anderson [3] reported that antioxidants can cause some visible biochemical and histopathological effects in decreasing severity of spinal cord traumas, but they do not diminish the clinical signs, that is, paralysis. Compression trauma of the cat spinal cord induces a very rapid alteration in the lipid metabolism of cellular membranes, including lipid hydrolysis with release of fatty acids including arachidonate, production of biologically active eicosanoids, and loss of cholesterol. This disturbance of cellular membranes can directly damage cells and can lead to the secondary development of tissue ionic imbalance, ischemia, edema, and inflammation with neuro-nophagia. Pretreatment with either the synthetic glucocorticoid methylprednisolone sodium succinate (MPSS) or the antioxidants vitamin E and selenium (Se) completely prevented the loss of cholesterol and partially inhibited lipolysis and prostanoid production. Treatment with only MPSS significantly reduced the postinjury tissue necrosis and paralysis [3].

Moreover, according to Coates et al. [22], the antioxidant 21-aminosteroid compound was also significantly effective in this disorder. Although significant differences in some portions of the neurological and histopathological examinations were observed, clinical efficacy for the 21-aminosteroid compound (U74389G) could not be established in acute-compressive spinal cord trauma at the second lumbar spinal cord segment (100 g, 300 s) of dogs [22].

Lucas [72] examined the level of different LPO products, such as hydroxyalkenals (4-HAs) and MDA after spinal cord injury. They used a specific treatment against them, such as the GSH precursor γ -glutamylcysteine. These authors mention that 4-HAs are much more reactive than MDA and are considered among the most toxic LPO products. After spinal cord injury, spinal cord irrigation with γ -glutamylcysteine preserved GSH and reduced 4-HAs below naive levels but had no effect on MDA. By 24 h after spinal cord injury, MDA returned to naive levels but 4-HAs were still elevated. Once again, γ -glutamylcysteine treatment reduced 4-HAs elevation [72].

Bovine Mastitis

We can say that “*Aliena capella gerit distentius uber* (The udder of another’s gout is more distended;” Horace 65–8 BC), which means that another’s gout is better than ours, but not in the case when this distension is caused by mastitis [51]. An important role played by acute phase response and oxidative status in inflammation of the mammary gland in cows as mastitis is associated with significantly higher concentrations of inflammatory and oxidative mediators in the cells and blood.

Aitken [1] proved that gene expression of the pro-oxidant, 15-lipoxygenase 1, which is known to increase during times of oxidative stress, also increased dramatically in mammary tissue from early lactation (EL, 15–28 day in milk) cows. Expression of the pro-inflammatory cytokines, IL-1 β , IL-6, and IL-8 did not change significantly during the periparturient period. Close positive correlations were found between several antioxidant enzymes (cytosolic GPX, thioredoxin reductase 1, and heme oxygenase-1) and vascular adhesion molecules (intercellular vascular adhesion molecule-1, vascular cell adhesion molecule-1) suggesting a protective response of these antioxidants to an enhanced proinflammatory state. Ability to control oxidative stress through the antioxidant enzymes in the future may modify the proinflammatory state of periparturient cows and reduce incidence and severity of some diseases such as mastitis [1]. Local as well as systemic inflammation might play important roles in increased mammary oxidative stress [63]. The protective effects of antioxidants in a context of neutrophil-induced damage to mammary epithelial cells were evaluated in vitro using a coculture model of activated bovine neutrophils and a bovine mammary epithelial cell line (MAC-T cells). When incubated with neutrophils activated by lipopolysaccharides and phorbol 12-myristate 13-acetate, MAC-T cells released large amounts of lactate dehydrogenase indicating significant cell damage. The addition of DMTU or bathocuproine disulfonic acid did not reduce the damage whereas catechin, deferoxamine, or glutathione ethyl ester significantly reduced neutrophil-induced cytotoxicity in a

dose-dependent manner. The effect of deferoxamine, an iron chelator, on the growth of *E. coli* and the ability of bovine neutrophils to phagocytose these bacteria were then assessed in vitro. Data showed that deferoxamine did not interfere with the phagocytic activity of neutrophils but inhibited growth of the bacteria. The results suggest that antioxidants may be effective tools for protecting mammary tissue against neutrophil-induced oxidative stress during bovine mastitis [68].

Chaiyotwittayakun [20] reported a study in which they used vitamin C in the treatment of mastitis. Mastitis was induced in eight nonpregnant Holstein cows by intramammary infusion of endotoxin. Two doses of 25 g of ascorbic acid were administered intravenously at 3- and 5-h postendotoxin challenge. The authors reported an increased milk production recovery (9% higher, $P < 0.02$) and tended to reduce the extent of rumen stasis [20].

The plasma selenium levels indicate the amount of circulating selenoproteins and selenoenzymes. These are important for the maintenance of the redox system, modulating the immune system and also for thyroid hormone metabolism. The thyroid gland is among the human tissues with the highest Se content per mass unit similar to other endocrine organs and the brain. Not only are all three deiodinases selenoenzymes, but within the thyroid gland there are several other selenoenzymes, which are important for the maintenance of normal thyroid function [36]. Selenoproteins involved in cellular antioxidative defense systems and redox control, such as the GPx and the thioredoxin reductase (TxnRd) family, are involved in protection of the thyroid gland from excess hydrogen peroxide and ROS produced by the follicles for biosynthesis of thyroid hormones. In addition, the three key enzymes involved in activation and inactivation of thyroid hormones, the iodothyronine deiodinases (DIO1,2,3), are selenoproteins with development, cell-, and pathology-related expression patterns [64]. The trace element selenium is also in the prosthetic group of selenium-dependent GPX. Therefore it affects the innate and the adaptive immune responses of the mammary gland through cellular and humoral activities.

Substantial research has been carried out on the effect of selenium on the immune function of the mammary gland and subsequent improvement in bovine udder health and mastitis control. Levels higher than current recommendations and Se-yeast (0.3 mg/kg diet dry matter) can potentially be used to enhance our capacity to modulate the physiological mechanisms of the bovine mammary gland to respond to infection [103]. In spite of this replacement of sodium selenite with an organic source of Se (Se yeast) in diets not suboptimal in basal Se concentrations did not improve Se status, uterine health, fertilization, or embryo quality in early lactation dairy cows [19].

References

1. Aitken SL, Karcher EL, Rezamand P, Gandy JC, VandeHaar MJ, Capuco AV, Sordillo LM. Evaluation of antioxidant and proinflammatory gene expression in bovine mammary tissue during the periparturient period. *J Dairy Sci.* 2009;92(2):589–98.
2. Albanese F, Tieghi C, De Rosa L, Colombo S, Abramo F. Feline perforating dermatitis resembling human reactive perforating collagenosis: clinicopathological findings and outcome in four cases. *Vet Dermatol.* 2009;20(4):273–80.

3. Anderson DK, Saunders RD, Demediuk P, Dugan LL, Braughler JM, Hall ED, Means ED, Horrocks LA. Lipid hydrolysis and peroxidation in injured spinal cord: partial protection with methylprednisolone or vitamin E and selenium. *Cent Nerv Syst Trauma*. 1985;2(Winter 4):257–67.
4. Andreone P, Fiorino S, Cursaro C, et al. Vitamin E as treatment for chronic hepatitis B – results of a randomized controlled pilot trial. *Antivir Res* 2001;49:75–81.
5. Arvidsson S, Fält K, Haglund U. Feline *E. coli* bacteremia – effects of misoprostol/scavengers or methylprednisolone on hemodynamic reactions and gastrointestinal mucosal injury. *Acta Chir Scand*. 1990;156(3):215–21.
6. Asaba K, Iwasaki Y, Asai M, Yoshida M, Nigawara T, Kambayashi M, Hashimoto K. High glucose activates pituitary proopiomelanocortin gene expression: possible role of free radical-sensitive transcription factors. *Diabetes Metab Res Rev*. 2007;23(4):317–23.
7. Bakker J, Zhang H, Depierreux M, van Asbeck S, Vincent JL. Effects of N-acetylcysteine in endotoxic shock. *J Crit Care*. 1994;9(4):236–43.
8. Beck-Speier I, Dayal N, Karg E, Maier KL, Schumann G, Semmler M, Koelsch SM. Oxymetazoline inhibits proinflammatory reactions: effect on arachidonic acid-derived metabolites. *J Pharmacol Exp Ther*. 2006;316(2):843–51. Epub 2005 Oct 12.
9. Berglundh T, Lindhe J. Gingivitis in young and old dogs. *J Clin Periodontol* 1993;20:179–85.
10. Bishop A. Role of oxygen in wound healing. *J Wound Care*. 2008;17(9):399–402, Review.
11. Blake DR, Hall ND, Bacon PA, Dieppe PA, Halliwell B, Gutteridge JM. Effect of a specific iron chelating agent on animal models of inflammation. *Ann Rheum Dis*. 1983;42(1):89–93.
12. Bochsler PN, Slauson DO. Chapter 4: Inflammation and repair of tissue. In: Slauson DO, Cooper BJ, eds, *Mechanisms of Disease: A Textbook of Comparative General Pathology*, Third edition. MO, St. Louis: Elsevier (2002); pp 141–245.
13. Boerema I, Meyne NG, Brummelkamp WK, et al. Life without blood: a study of the influence of high atmospheric pressure and hypothermia on dilution of blood. *J Cardiovasc Surg*. 1960;1:133–46.
14. Boileau C, Martel-Pelletier J, Caron J, Msika P, Guillou GB, Baudouin C, Pelletier JP. Protective effects of total fraction of avocado/soybean unsaponifiables on the structural changes in experimental dog osteoarthritis: inhibition of nitric oxide synthase and matrix metalloproteinase-13. *Arthritis Res Ther*. 2009;11(2):R41. Epub 2009 Mar 16.
15. Bouachour G, Cronier P, Gouello JP et al. Hyperbaric oxygen therapy in the management of crush injuries: a randomized double blind placebo-controlled clinical trial. *J Trauma*. 1996;41:333–9.
16. Boykin JV Jr, Baylis C. Hyperbaric oxygen therapy mediates increased nitric oxide production associated with wound healing: a preliminary study. *Adv Skin Wound Care*. 2007;20(7):382–8.
17. Buranakarl C, Trisiriroj M, Pondeenana S, Tungjitpeanpong T, Jarutakanon P, Penchome R. Relationships between oxidative stress markers and red blood cell characteristics in renal azotemic dogs. *Res Vet Sci*. 2009;86(2):309–13. Epub 2008 Jul 29.
18. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 2007;46(8):1223–33.
19. Cerri RL, Rutigliano HM, Lima FS, Araújo DB, Santos JE. Effect of source of supplemental selenium on uterine health and embryo quality in high-producing dairy cows. *Theriogenology*. 2009;71(7):1127–37. Epub 2009 Feb 1.
20. Chaiyotwittayakun A, Erskine RJ, Bartlett PC, Herd TH, Sears PM, Harmont RJ. The effect of ascorbic acid and L-histidine therapy on acute mammary inflammation in dairy cattle. *J Dairy Sci*. 2002;85(1):60–7.
21. Chon SK, Kim NS. Evaluation of silymarin in the treatment on asymptomatic *Giardia* infections in dogs. *Parasitol Res*. 2005;97(6):445–51.
22. Coates JR, Sorjonen DC, Simpson ST, Cox NR, Wright JC, Hudson JA, Finn-Bodner ST, Brown SA. Clinicopathologic effects of a 21-aminosteroid compound (U74389G) and high-dose methylprednisolone on spinal cord function after simulated spinal cord trauma. *Vet Surg*. 1995;24(2):128–39.

23. Dabrowski A, Gabryelewicz A, Chyczewski L. The effect of platelet activating factor antagonist (BN 52021) on cerulein-induced acute pancreatitis with reference to oxygen radicals. *Int J Pancreatol.* 1991;8(1):1–11.
24. Deaton CM, Marlin DJ, Smith NC, Roberts CA, Harris PA, Kelly FJ, Schroter RC. Pulmonary bioavailability of ascorbic acid in an ascorbate-synthesising species, the horse. *Free Radic Res.* 2003;37(4):461–7.
25. Dziezyc J, Millichamp NJ, Rohde BH, Baker JS, Chiou GC. Effects of lipoxygenase inhibitors in a model of lens-induced uveitis in dogs. *Am J Vet Res.* 1989;50(11):1877–82.
26. Elayan IM, Milton J. Effect of hyperbaric oxygen treatment on nitric oxide and oxygen free radicals in rat brain. *J Neurophysiol.* 2000;83:2022–9.
27. Escobar SJ, Slade JB Jr, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen therapy (HBO₂) for treatment of necrotizing fasciitis reduces mortality and amputation rate. *Undersea Hyperb Med.* 2005;32(6):437–43.
28. Fantone JC, Ward PA. Polymorphonuclear leukocyte-mediated cell and tissue injury: oxygen metabolites and their relations to human disease. *Hum Pathol.* 1985;16(10):973–8. Review.
29. Feldmeier JJ. Hyperbaric Oxygen Therapy 2003: Indications and Results. The Hyperbaric Oxygen Therapy Committee Report. Kensington, MD: Undersea and Hyperbaric Medical Society; 2003.
30. Ferrándiz ML, Sanz MJ, Bustos G, Payá M, Alcaraz MJ, De Rosa S. Avarol and avarone, two new anti-inflammatory agents of marine origin. *Eur J Pharmacol.* 1994;253(1–2):75–82.
31. Fliiss H, Ménard M. Hypochlorous acid-induced mobilization of zinc from metalloproteins. *Arch Biochem Biophys.* 1991;287(1):175–9.
32. Francis TJ, Dutka AJ, Hallenbeck JM. Pathophysiology of decompression sickness. In: Bove AA, Davis JC, eds. *Diving Medicine*. Philadelphia, PA: WB Saunders (1990); pp 170–87.
33. Frech TM, Clegg DO. The utility of nutraceuticals in the treatment of osteoarthritis. *Curr Rheumatol Rep.* 2007;9(1):25–30. Review.
34. Gabb G, Robin ED. Hyperbaric oxygen: a therapy in search of diseases. *Chest.* 1987;92:1074–82.
35. Garrett IR, Boyee BE, Orefito ROC, Bonewald L, Poser J, Mundy GR. Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone in vitro and in vivo. *J Clin Invest* 1990;85:632–9.
36. Gärtner R. Selenium and thyroid hormone axis in critical ill states: an overview of conflicting view points. *J Trace Elem Med Biol.* 2009;23(2):71–4. Epub 2009 Feb 25.
37. Gaspar MM, Boerman OC, Laverman P, Corvo ML, Storm G, Cruz ME. Enzymosomes with surface-exposed superoxide dismutase: in vivo behaviour and therapeutic activity in a model of adjuvant arthritis. *J Control Release.* 2007;117(2):186–95. Epub 2006 Nov 10.
38. Gimbel ML, Hunt TK. Wound healing and hyperbaric oxygenation. In: EP Kindwall (ed.), *Hyperbaric Medicine Practice*. Flagstaff, AZ: Best Publishing (2002); pp 169–204.
39. Gomez-Cambronero L, Camps B, de La Asuncion JG, Cerda M, Pellin A, Pallardo FV, Calvete J, Sweiry JH, Mann GE, Vina J, Sastre J. Pentoxifylline ameliorates cerulein-induced pancreatitis in rats: role of glutathione and nitric oxide. *J Pharmacol Exp Ther.* 2000;293(2):670–6. L 2000.
40. Gross V, Arndt H, Andus T, Palitzsch KD, Scholmerich J. Free radicals in inflammatory bowel diseases pathophysiology and therapeutic implications. *Hepatogastroenterology.* 1994;41(4):320–7. Review.
41. Guy J, McGorray S, Qi X, Fitzsimmons J, Mancuso A, Rao N. Conjugated deferoxamine reduces blood-brain barrier disruption in experimental optic neuritis. *Ophthalmic Res.* 1994;26(5):310–23.
42. Halliwell B. Drug antioxidant effects: A basis for drug selection? *Drugs.* 1991;42(4):569–605.
43. Henderson A, Hayes P. Acetylcysteine as a cytoprotective antioxidant in patients with severe sepsis: potential new use for an old drug. *Ann Pharmacother.* 1994;28(9):1086–8.
44. Henrotin Y, Kurz B. Antioxidant to treat osteoarthritis: dream or reality? *Curr Drug Targets.* 2007;8(2):347–57. Review.

45. Hillman JD, Socransky SS. Replacement therapy of the prevention of dental disease. *Adv Dent Res*. 1987;1(1):119–25.
46. Hilton JG. Effects of alterations of polyunsaturated fatty acid metabolism upon plasma volume loss induced by thermal trauma. *J Trauma*. 1980;20(8):663–9.
47. Hippocrates. Aphorisms. Section VII. Translated by Francis Adams, The Internet Classics Archive by Daniel C. Stevenson, Web Atomics. World Wide Web presentation is copyright (C) 1994–2000, Daniel C. Stevenson, Web Atomics. Point: 87, 400 BC.
48. Hitt ME. Chronic active hepatitis in dogs – experiences with aggressive treatment efforts. In: 2001 Proceedings, 19th Annual American College of Veterinary Internal Medicine Forum. Denver, CO, American College of Veterinary Internal Medicine, 2001, pp 775–7.
49. Horatius Quintus Flaccus. (Horace). Epistles I.18, 80. 20–14 BC. H. Rushton Fairclough, Horace. Satires, Epistles, and Ars Poetica. The Harvard University Press, Cambridge, MA 1978
50. Horatius Quintus Flaccus. (Horace). Odes I, 11.8. 23–13 BC H. Rushton Fairclough, Horace. Satires, Epistles, and Ars Poetica The Harvard University Press, Cambridge, MA 1978.
51. Horatius Quintus Flaccus. (Horace). Satires, 35–20 BC H. Rushton Fairclough, Horace. Satires, Epistles, and Ars Poetica The Harvard University Press, Cambridge, MA 1978.
52. Hunt TK, Niinikoski J, Zederfeldt BH. Oxygen in wound healing enhancement: cellular effects of Oxygen, In: Davis JC, Hunt TK, eds, Hyper Baric Therapy. Bethesda, MD: The Undersea Medical Society, 1977;111–22.
53. Inokuchi T, Kawamoto T, Aoki K, Aoki A, Nagahama K, Baba Y, Suzuki S, Shibayama M, Mano Y, Ohya K, Moriyama K. The effects of hyperbaric oxygen on tooth movement into the regenerated area after distraction osteogenesis. *Cleft Palate Craniofac J*. 2009;14:1.
54. Isik AT, Mas MR, Yamanel L, Aydin S, Comert B, Akay C, Erdem G, Mas N. The role of allopurinol in experimental acute necrotizing pancreatitis. *Indian J Med Res*. 2006;124(6):709–14.
55. Itoh S, Ozumi K, Kim HW, Nakagawa O, McKinney RD, Folz RJ, Zelko IN, Ushio-Fukai M, Fukai T. Novel mechanism for regulation of extracellular SOD transcription and activity by copper: role of antioxidant-1. *Free Radic Biol Med*. 2009;46(1):95–104.
56. Jacobs BP, Dennehy C, Ramirez G, et al: Milk thistle for the treatment of liver disease – a systematic review and meta-analysis. *Am J Med* 2002;113:506–15.
57. Jonkam CC, Bansal K, Traber DL, Hamahata A, Maybauer MO, Maybauer DM, Cox RA, Lange M, Connelly RL, Traber LD, Djukom CD, Salsbury JR, Herndon DN, Enkhbaatar P. Pulmonary vascular permeability changes in an ovine model of methicillin-resistant *Staphylococcus aureus* sepsis. *Crit Care*. 2009;13(1):R19.
58. Kalil AC, Sevransky JE, Myers DE, Esposito C, Vandivier RW, Eichacker P, Susla GM, Solomon SB, Csako G, Costello R, Sittler KJ, Banks S, Natanson C, Danner RL. Preclinical trial of L-arginine monotherapy alone or with N-acetylcysteine in septic shock. *Crit Care Med*. 2006;34(11):2719–28.
59. Keshavarzian A, Morgan G, Sedghi S, Gordon JH, Doria M. Role of reactive oxygen metabolites in experimental colitis. *Gut*. 1990;31(7):786–90.
60. Khanna D, Sethi G, Ahn KS, Pandey MK, Kunnumakkara AB, Sung B, Aggarwal A, Aggarwal BB. Natural products as a gold mine for arthritis treatment. *Curr Opin Pharmacol*. 2007;7(3):344–51. Epub 2007 May 1. Review.
61. Kirk GR, White JS, McKie L, Stevenson M, Young I, Clements WD, Rowlands BJ. Combined antioxidant therapy reduces pain and improves quality of life in chronic pancreatitis. *J Gastrointest Surg*. 2006;10(4):499–503.
62. Kirschvink N, Smith N, Fievez L, Bougnet V, Art T, Degand G, Marlin D, Roberts C, Genicot B, Lindsey P, Lekeux P. Effect of chronic airway inflammation and exercise on pulmonary and systemic antioxidant status of healthy and heaves-affected horses. *Equine Vet J*. 2002;34(6):563–71.
63. Kleczkowski M, Kluciiński W, Jakubowski T, Sikora J. Dependence between acute phase response, oxidative status and mastitis of cows. *Pol J Vet Sci*. 2006;9(2):151–8.
64. Köhrle J, Gärtner R. Selenium and thyroid. *Best Pract Res Clin Endocrinol Metab*. 2009;23(6):815–27.

65. Kramaric P, Pavlica Z, Koklic T, Nemec A, Erzen NK, Sentjurs M. Membrane switch hypothesis. 2. Domain structure of phagocytes in horses with recurrent airway obstruction. *J Chem Inf Model*. 2005;45(6):1708–15.
66. Lange M, Enkhbaatar P, Nakano Y, Traber DL. Role of nitric oxide in shock: the large animal perspective. *Front Biosci*. 2009;14:1979–89.
67. Lapenna D, De Gioia S, Ciofani G, Mezzetti A, Consoli A, Di Ilio C, Cuccurullo F. Hypochlorous acid-induced zinc release from thiolate bonds: a potential protective mechanism towards biomolecules oxidant damage during inflammation. *Free Radic Res*. 1994;20(3):165–70.
68. Lauzon K, Zhao X, Bouetard A, Delbecchi L, Paquette B, Lacasse P. Antioxidants to prevent bovine neutrophil-induced mammary epithelial cell damage. *J Dairy Sci*. 2005;88(12):4295–303.
69. Lee JJ, Son HY, Kim MC. Attenuation of ischemia-reperfusion injury by ascorbic acid in the canine renal transplantation. *J Vet Sci*. 2006;7(4):375–9.
70. Leveille CR, Arias IM. Pathophysiology and pharmacologic modulation of hepatic fibrosis. *J Vet Intern Med* 1993;7:73–84.
71. Lewis DD, Church DF, Hosgood G and van Ee RT. Investigation of oxygen-derived free radical generation in cancellous bone specimens obtained from dogs. *AJVR* 1994;55:1608–12.
72. Lucas JH, Wheeler DG, Guan Z, Suntres Z, Stokes BT. Effect of glutathione augmentation on lipid peroxidation after spinal cord injury. *J Neurotrauma*. 2002;19(6):763–75.
73. Lucretius Titus Carus. *De rerum natura*. Concordances of Lucretius, 5.1284 50 BC.
74. Lyon KC. The case for evidence in wound care: investigating advanced treatment modalities in healing chronic diabetic lower extremity wounds. *J Wound Ostomy Continence Nurs*. 2008;35(6):585–90.
75. Mao GD, Thomas ED, Lopaschuk GD, Poznansky MJ. Superoxide dismutase (SOD)-catalase conjugates. *J Biol Chem* 1993;268:416–20.
76. Martindale VE, McKay K. Hyperbaric oxygen treatment of dogs has no effect on red cell deformability but causes an acute fluid shift. *Physiol Chem Phys Med NMR*. 1995;27(1):45–53.
77. Matejovic M, Krouzecky A, Martinkova V, Rokyta R Jr, Radej J, Kralova H, Treska V, Radermacher P, Novak I. Effects of tempol, a free radical scavenger, on long-term hyperdynamic porcine bacteremia. *Crit Care Med*. 2005;33(5):1057–63.
78. Mathy-Hartert M, Hogge L, Sanchez C, Deby-Dupont G, Crielard JM, Henrotin Y. Interleukin-1beta and interleukin-6 disturb the antioxidant enzyme system in bovine chondrocytes: a possible explanation for oxidative stress generation. *Osteoarthritis Cartil*. 2008;16(7):756–63.
79. McCord JM, Wong K, Stokes SH, Petrone WF, English D. Superoxide and inflammation: a mechanism for the anti-inflammatory activity of superoxide dismutase. *Acta Physiol Scand Suppl*. 1980;492:25–30.
80. Michelson AM, Puget K. Anti inflammatory activity of superoxide dismutases: comparison of enzymes from different sources in different models in rats: mechanism of action. *Free Radic Res Commun*. 1986;2:43–56.
81. Mink SN, Kasian K, Santos Martinez LE, Jacobs H, Bose R, Cheng ZQ, Light RB. Lysozyme, a mediator of sepsis that produces vasodilation by hydrogen peroxide signaling in an arterial preparation. *Am J Physiol Heart Circ Physiol*. 2008 Apr;294(4):H1724–35. Epub 2008 Feb 8.
82. Misaki H, Suzuki M, Yoshie H, Se Hara K. The effect of superoxide dismutase on the inflammation induced by periodontal pathogenic bacteria and wound healing of gingival incision. *J Jpn Assoc Periodontol* 1990;32, 93–100.
83. Niinikoski J. Effect of oxygen supply on wound healing and formation of experimental granulation tissue. *Acta Physiol Scand Suppl* 1969;334:1.
84. Nylander G, Nordstrom H, Eriksson E. Effects of hyperbaric oxygen on edema formation after a scald burn. *Burns*, 1984;10(3):193–6.
85. Nylander G, Lewis DH, Nordstrom HR. Reduction of post ischemic edema with hyperbaric oxygen. *Plast Reconstr Surg*. 1985;76:596–601.

86. Oury TD, Ho Y, Piantadosi CA. Extracellular superoxide dismutase, nitric oxide, and central nervous system O₂ toxicity. *Proc Natl Acad Sci* 1992;89:9715–19.
87. Ovidius Publius Naso. *Grave carving*. 3.3.73–76. 10 CE.
88. Pakman LM. Inhibition of *Pseudomonas aeruginosa* by hyperbaric oxygen. I. Sulfonamide activity enhancement and reversal. *Infect Immun*. 1971;4:479–87.
89. Paquette DW, Rosenberg A, Lohinai Z, Southan GJ, Williams RC, Offenbacher S, Szabo C. Inhibition of experimental gingivitis in beagle dogs with topical mercaptoalkylguanidines. *J Periodontol*. 2006;77(3):385–91.
90. Paracelsus – *Collected Writings Vol. I* (1926) edited by Bernhard Aschner, p 110.
91. Park MK. Effects of hyperbaric oxygen in infectious diseases: basic mechanisms. In: Kindwall EP, ed, *Hyperbaric Medicine Practice*. Flagstaff, AZ: Best Publishing (2002); pp 205–44.
92. Park MK, Muhvich KH, Myers RAM. Hyperoxia prolongs the aminoglycoside-induced post antibiotic effect in *pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 1991;35:691–5.
93. Petelin M, Pavlica Z, Ivanusa T, Sentjurc M, Skaleric U. Local delivery of liposome-encapsulated superoxide dismutase and catalase suppress periodontal inflammation in beagles. *Clin Periodontol*. 2000;27(12):918–25.
94. Peuchant E, Beauvieux MCD, Dubourg L, Thomas MJ, Perromat A, Aparicio M, Clerc M, Combe C. Antioxidant effects of a supplemented very low protein diet in chronic renal failure. *Free Radic Biol Med*. 1997;22(1–2): 313–20.
95. Qi X, Sun L, Lewin AS, Hauswirth WW, Guy J. Long-term suppression of neurodegeneration in chronic experimental optic neuritis: antioxidant gene therapy. *Invest Ophthalmol Vis Sci*. 2007;48(12):5360–70.
96. Rao NA, Romero JL, Fernandez MA, Sevanian A, Marak GE Jr. Effect of iron chelation on severity of ocular inflammation in an animal model. *Arch Ophthalmol*. 1986;104(9):1369–71.
97. Rao NA, Sevanian A, Fernandez MA, Romero JL, Faure JP, de Kozak Y, Till GO, Marak GE Jr. Role of oxygen radicals in experimental allergic uveitis. *Invest Ophthalmol Vis Sci*. 1987;28(5):886–92.
98. Ries WL, Key LL, Rodriguez RM. Nitroblue tetrazolium reduction and bone resorption by osteoclasts in vitro inhibited by a manganese-based superoxide dismutase mimic. *J Bone Miner Res* 1992;7:931–9.
99. Risber J, Tyssebotn I. Hyperbaric exposure to a 5 ATA He-[N.sub.2]-[O.sub.2] atmosphere affects the cardiac function and organ blood flow distribution in awake trained rats. *Undersea Biomed Res*. 1986;13:77–90.
100. Rosenthal RE, Silbergleit R, Hof PR, Haywood Y, Fiskum G. Hyperbaric oxygen reduces neuronal death and improves neurological outcome after canine cardiac arrest. *Stroke*. 2003 May;34(5):1311–16.
101. Rump AF, Siekmann U, Kalff G. Effects of hyperbaric and hyperoxic conditions on the disposition of drugs: theoretical considerations and a review of the literature. *Gen Pharmacol*. 1999;32(1):127–33.
102. Salahudeen AK, Wang C, Bigler SA, Dai Z, Tachikawa H. Synergistic renal protection by combining alkaline-diuresis with lipid peroxidation inhibitors in rhabdomyolysis: possible interaction between oxidant and non-oxidant mechanisms. *Nephrol Dial Transplant*. 1996;11(4):635–42.
103. Salman S, Khol-Parisini A, Schafft H, Lahrssen-Wiederholt M, Hulan HW, Dinse D, Zentek J. The role of dietary selenium in bovine mammary gland health and immune function. *Anim Health Res Rev*. 2009;10(1):21–34. Epub 2009 Feb 6. Review.
104. Santos L, Tipping PG. Attenuation of adjuvant arthritis in rats by treatment with oxygen radical scavengers. *Immunol Cell Biol*. 1994;72(5):406–14.
105. Schoenberg MH, Büchler M, Baczako K, Bültmann B, Younes M, Gasper M, Kirchmayr R, Beger HG. The involvement of oxygen radicals in acute pancreatitis. *Klin Wochenschr*. 1991;69(21–23):1025–31.
106. Schuller-Levis GB, Levis WR, Ammazalorso M, Nosrati A, Park E. Mycobacterial lipoarabinomannan induces nitric oxide and tumor necrosis factor alpha production in a macrophage cell line: down regulation by taurine chloramine. *Infect Immun*. 1994;62(10):4671–4.

107. Sener G, Aksoy H, Sehirli O, Yüksel M, Aral C, Gedik N, Cetinel S, Yeğen BC. Erdosteine prevents colonic inflammation through its antioxidant and free radical scavenging activities. *Dig Dis Sci*. 2007;52(9):2122–32.
108. Shaw FL, Handy RD, Bryson P, Sneyd JR, Moody AJ. A single exposure to hyperbaric oxygen does not cause oxidative stress in isolated platelets: no effect on superoxide dismutase, catalase, or cellular ATP. *Clin Biochem*. 2005;38(8):722–6.
109. Sheffield PJ, Smith AP. Physiological and pharmacological basis of hyperbaric oxygen therapy. In: DJ Bakker, ed., *Hyperbaric Surgery: Perioperative Care*. Flagstaff, AZ: Best Publishing (2002); pp 63–110.
110. Sheffield JC, Sheffield PJ, Ziemba AL. Complications rates of HBO treatments: a 21-year analysis. *Proceedings of XIV International Congress on Hyperbaric Medicine*. Flagstaff, AZ: Best Publishing, 2002.
111. Sifton DW, ed. *Physicians' Desk Reference* (ed 56). Montvale, NJ: Medical Economics Co. Inc.; 2002.
112. Singh D, Kumar P, Majumdar S, Narang A. Effect of phenobarbital on free radicals in neonates with hypoxic ischemic encephalopathy – a randomized controlled trial. *J Perinat Med*. 2004;32(3):278–81.
113. Siriwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, Hardman JG, Jamdar S. Randomized, double-blind, placebo-controlled trial of intravenous antioxidant (n-acetylcysteine, selenium, vitamin c) therapy in severe acute pancreatitis. *Gut*. 2007; 56(10):1439–1444.
114. Slovis N. Review of Hyperbaric Medicine. *Veterinary Hyperbaric Medicine Society*. University of Tennessee, College of Veterinary Medicine. <http://www.vet.utk.edu/vhms/review.html>. 2006.
115. Snapper JR, Bernard GR, Brigham KL. In vivo oxidants and pulmonary inflammation. *Bull Eur Respir Pathol Respir*. 1986;22(1):257s–60s.
116. Sokol RJ, Twedt D, McKim JM, et al. Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis. *Gastroenterology* 1994;107:1788–98.
117. Spee B, Arends B, van den Ingh TS, Penning LC, Rothuizen J. Copper metabolism and oxidative stress in chronic inflammatory and cholestatic liver diseases in dogs. *J Vet Intern Med*. 2006;20(5):1085–92.
118. Stahelin H, Karnovsky ML, Farnham AE, Suter E. Studies on the interaction between phagocytes and tubercle bacilli: III. Some metabolic effects in guinea pigs associated with infection with tubercle bacilli. *J Exp Med*. 1957;105(3):265–77.
119. Szabolcs A, Varga IS, Varga C, Berko A, Kaszaki J, Letoha T, Tiszlavicz L, Sari R, Lonovics J, Takacs T. Beneficial effect of resveratrol on cholecystokinin-induced experimental pancreatitis. *Eur J Pharmacol*. 2006;532(1–2):187–93.
120. Taubert D, Berkels R, Grosser N, Schroder H, Grundemann D, Schomig E. Aspirin induces nitric oxide release from vascular endothelium: a novel mechanism of action. *Br J Pharmacol*. 2004;143(1):159–65. Epub 2004 Aug 2.
121. Terentius Varro, Marcus. <http://audiolatinproverbs.blogspot.com/2007/04/facile-omnes-cum-valemus-recta-consilia.html>. Latin Via Proverbs, Dictum sapienti sat est. April 08, 2007.
122. Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: critical review of its current use in cosmetic and clinical dermatology. *Dermatol Surg*. 2005;31(7 Pt 2):805–13; discussion 813. Review.
123. Thom SR, Mendiguren I, Hardy K, Bolotin T. Inhibition of human neutrophil beta2-integrin-dependent adherence by hyperbaric O₂. *Am J Physiol*. 1997;26:82–6.
124. Trachtman H, Chan JC, Chan W, Valderrama E, Brandt R, Wakely P, Futterweit S, Maesaka J, Ma C. Vitamin E ameliorates renal injury in an experimental model of immunoglobulin A nephropathy. *Pediatr Res*. 1996;40(4):620–6.
125. Tsiakitzis K, Kourounakis AP, Tani E, Rekka EA, Kourounakis PN. Stress and active oxygen species – effect of alpha-tocopherol on stress response. *Archiv der Pharmazie* 2005;338(7):315–21.

126. Turrens JF, Craps JD, Freeman BA. Protection against oxygen toxicity by intravenous injection of liposomal-en trapped catalase and superoxide dismutase. *J Clin Invest* 1984;73:87–95.
127. Twedt DC. Nutraceuticals for liver dysfunction. In: 2003 Proceedings, North American Veterinary Conference. Orlando, FL, Eastern States Veterinary Association, 2003, pp 434–6.
128. Twedt DC. Antioxidants and liver disease. In: 2001 Proceedings, 19th Annual American College of Veterinary Internal Medicine Forum. Denver, CO, American College of Veterinary Internal Medicine, 2001a, pp 13–15.
129. Twedt DC. A review of traditional and not so traditional therapies for liver disease. In: 2001 Proceedings, 19th Annual American College of Veterinary Internal Medicine Forum. Denver, CO, American College of Veterinary Internal Medicine, 2001b, pp 610–12.
130. Vajdovich P. Free radicals and antioxidants in inflammatory processes and ischemia-reperfusion injury. *Vet Clin North Am Small Anim Pract.* 2008 Jan;38(1):31–123, v. Review.
131. Váradi Á. Preliminary data of life and health insurance in the Roman law (Collegium funeraticum and collegium tenuiorum) *Hungarian Med J* 2008;2(4):533–8.
132. Vassilev D, Hauser B, Bracht H, Iványi Z, Schoaff M, Asfar P, Vogt J, Wachter U, Schelzig H, Georgieff M, Brückner UB, Radermacher P, Fröba G. Systemic, pulmonary, and hepatoplanchnic effects of N-acetylcysteine during long-term porcine endotoxemia. *Crit Care Med.* 2004;32(2):525–32.
133. Verspaget HW, Mulder TP, Veer A, Peña AS, Lamers CB. Reactive oxygen metabolites and colitis: a disturbed balance between damage and protection, A selective review. *Scand J Gastroenterol Suppl.* 1991;188:44–51.
134. Vogel G, Tuchweber B, Trost W, et al. Protection by silibinin against *Amanita phalloides* intoxication in beagles. *Toxicol Appl Pharmacol* 1984;73:355–62.
135. Wallace KP, Center SA, Hickford FH, et al. S-adenosyl-L-methionine (SAME) for the treatment of acetaminophen toxicity in a dog. *J Am Anim Hosp Assoc* 2002;38:246–54.
136. Wang X, Ding I, Xie H. Hyperbaric oxygen and basic fibroblast growth factor promote growth of irradiated bone. *Growth Factors* 1995;12(1): 29–35.
137. Williams DL, Munday P. The effect of a topical antioxidant formulation including N-acetyl carnosine on canine cataract: a preliminary study. *Vet Ophthalmol.* 2006;9(5):311–16.
138. Wu GS, Walker J, Rao NA. Effect of deferoxamine on retinal lipid peroxidation in experimental uveitis. *Invest Ophthalmol Vis Sci.* 1993;34(11):3084–9.
139. Yamada M, Shichi H, Yuasa T, Tanouchi Y, Mimura Y. Superoxide in ocular inflammation: human and experimental uveitis. *J Free Radic Biol Med.* 1986;2(2):111–17.
140. Yoles E, Zurovsky Y, Zarchin N, Mayevsky A. The effect of hyperbaric hyperoxia on brain function in the newborn dog in vivo. *Neurol Res.* 2000;22(4):404–8.
141. Yoshikawa T, Takahashi S, Kondo M. Possible role of free radicals in the chronic inflammation of the gut. *EXS.* 1992;62:353–8.
142. Zamboni WA, Wong HP. Effect of hyperbaric oxygen on neutrophil concentration and pulmonary sequestration in reperfusion injury. *Arch Surg* 1996;131:756–60.
143. Zhang H, Spapen H, Manikis P, Rogiers P, Metz G, Buurman WA, Vincent JL. Tirilazad mesylate (U-74006F) inhibits effects of endotoxin in dogs. *Am J Physiol.* 1995;268(5 Pt 2):H1847–55.
144. Zhao LL, Davidson JD, Wee SC. Effect of hyperbaric oxygen and growth factors on rabbit ear ischemic ulcers. *Int J Radiat Oncol Biol Phys* 1998;40(1):189–96.
145. Babizhayev MA. Biological activities of the natural imidazole-containing peptidomimetics n-acetylcarnosine, carnosine and L-carnosine in ophthalmic and skin care products. *Life Sci.* 2006;78(20):2343–57.
146. Cruz ME, Manuela Gaspar M, Bárbara M, Martins F, Luísa Corvo M. Liposomal superoxide dismutases and their use in the treatment of experimental arthritis. *Methods Enzymol.* 2005;391:395–413.
147. Gathwala G, Marwah A, Gahlaut V, Marwah P. Effect of High-dose Phenobarbital on Oxidative Stress in Perinatal Asphyxia: An Open Label Randomized Controlled Trial. *Indian Pediatr.* 2010 Nov 30. pii: S097475590900675-1.
148. Honeckman A. Current concepts in the treatment of canine chronic hepatitis. *Clin Tech Small Anim Pract.* 2003 Nov;18(4):239–44.



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