Oxidative stress is a medical term for damage to animal or plant cells (and thereby the organs and tissues composed of those cells) caused by reactive oxygen species, which include (but are not limited to) superoxide, singlet oxygen, peroxynitrite or hydrogen peroxide.

It is defined as an imbalance between pro-oxidants and anti-oxidants, with the former prevailing.

Oxidative stress is known to contribute to tissue injury following irradiation and hyperxia and is thought to be a cause of neurodegenerative diseases including Lou Gehrig’s disease (aka MND or ALS), Parkinson’s disease, Alzheimer’s disease and Huntington’s disease. Oxidative stress is thought to be linked to certain cardiovascular disease, since oxidation of LDL in the endothelium is a precursor to plaque formation.

Superoxide, is produced deleteriously by 1-electron transfers in the mitochondrial electron transfer chain. Other enzymes capable of producing superoxide are xanthine oxidase, NADPH oxidases and cytochrome P450(s). Hydrogen peroxide is produced by a wide variety of enzymes including monoxygenases and oxidases.

Reactive oxygen species may also play a role in cell signaling.

Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) include oxygen ions, free radicals and peroxides both inorganic and organic.

They are generally very small molecules and are highly reactive due to the presence of unpaired valence shell electrons. ROSs form as a natural byproduct of the normal metabolism of oxygen but can damage cell membranes by causing oxidative stress. Cells are normally able to defend themselves against ROS damage through the use of the enzymes superoxide dismutase (SOD) and catalase.

The effects of ROS on cell metabolism have been well documented in a variety of species. These include not only roles in programmed cell death and apoptosis, but also positive effects such as the induction of host defense genes and mobilisation of ion transport systems. This is implicating them more frequently with roles in oxidative signalling. In particular, platelets involved in wound repair and blood homeostasis release ROS to recruit additional platelets to sites of injury. These also provide a link to the adaptive immune system via the recruitment of leukocytes.

Reactive oxygen species are implicated in cellular activity to a variety of inflammatory responses including cardiovascular disease and hearing impairment via cochlear damage induced by elevated sound levels. Sen, C.K. (2003) The general case for redox control of wound repair, Wound Repair and Regeneration, 11, 431-438


The enzyme superoxide dismutase (SOD, EC 1.15.1.1) catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. As such, it is an important antioxidant defense in nearly all cells exposed to oxygen. One of the exceedingly rare exceptions is Lactobacillus plantarum and related lactobacilli.

**Human**

In humans, three forms of superoxide dismutase are present. SOD1 is located in the cytoplasm, SOD2 in the mitochondria and SOD3 is extracellular. The first is a dimer (consists of two units), while the others are tetramers (four subunits). SOD1 and SOD3 contain copper and zinc, while SOD2 has manganese in its active center. The genes are located on chromosomes 21, 6 and 4, respectively (21q22.1, 6q25.3 and 4p15.3-p15.1).

**Physiology**

The superoxide anion radical (O2) spontaneously dismutates to O2 and H2O2 quite rapidly. However, SOD has the fastest turnover number (reaction rate with its substrate) of any known enzyme. In fact, its rate is diffusion-limited. Thus, under real-world intracellular conditions, SOD greatly reduces the ambient level of the dangerous superoxide radical.

The presence of SOD has been shown to help protect many types of cells from the free radical damage that is important in aging, senescence, and ischemic tissue damage. SOD also helps protect cells from DNA damage, lipid peroxidation, ionizing radiation damage, protein denaturation, and many other forms of progressive cell degradation.

**Further Reading**

Superoxide dismutase (SOD) catalyzes the destruction of the O2-free radical. It protects oxygen-metabolizing cells against harmful effects of superoxide free-radicals (Petkau et al. 1975; Fridovich 1972, 1973; Lavelle et al. 1973; Paschen and Weser 1973). It has been reviewed by Malmström et al. (1975).

McCord (1974) found that SOD protects hyalurionate against depolymerization by free-radicals and indicated that exogenous SOD might have an anti-inflammatory effect (Salin and McCord 1975). The O2- ion, which has been considered important in aging, lipid peroxidation and the peroxidative hemolysis of red blood cells (Fee and Teitelbaum 1972), is formed by the univalent reduction of O2 during various enzymatic reactions or by ionizing radiation. (See also Fee et al. 1975). There is also superoxide radical formation during leukocyte phagocytosis (Allen et al. 1974; DeChatelet et al. 1974). See also Dionisi et al. (1975). Winterbourn et al. (1975) indicate that SOD deficiency might lead to Heinz body hemolytic anemia. Fridovich (1986) reports on the biological effects of the superoxide radical.

Superoxide dismutase is widespread in nature. Gregory et al. (1974) indicate it to be present in all oxygen-metabolizing cells. Hewitt and Morris (1975) have found it in anaerobic bacteria. It has been purified from diverse sources such as fungi (Rapp et al. 1973); green pea (Sawda et al. 1972); Streptococcus mutans (Vance et al. 1972); wheat germ (Beauchamp and Fridovich 1973); E. coli (Gregory et al. 1973); Saccharomyces cerevisiae (Goscin and Fridovich 1972) and Neospora crassa (Misra and Fridovich 1972).

**References**

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Fridovich, I.: Superoxide Radical and Superoxide Dismutase, Biochem Soc Trans 1, 48, 1973

Fridovich, I.: Biological Effects of the Superoxide Radical, Arch Biochem Biophys 247, 1, 1986


Paschen, W., and Weser, U.: Singlet Oxygen Decontaminating

[Continued on page 7]
The body constantly reacts with oxygen as part of the energy producing processes of cells. As a consequence of this activity, highly reactive molecules are produced known as free radicals.

These interact with other molecules within the cell, which can cause oxidative damage to proteins, membranes, and genes. This damage has been implicated in the cause of certain diseases and has an impact on the body’s aging process.

**Antioxidants**

It’s the job of antioxidants to neutralize free radicals, and the body produces an armory of them to defend itself. The metabolic processes that produce antioxidants are controlled and influenced by an individual’s genetic make-up and the extra environmental factors (such as diet, smoking, and pollution) to which the body is exposed.

Unfortunately, changes in our lifestyles, which include more environmental pollution and less quality in our diets, mean that we are exposed to more free radicals than ever before.

Our internal production of antioxidants is insufficient to neutralize and scavenge all the free radicals, but there is an abundant supply of antioxidants in a wide variety of foods.

By increasing our dietary intake of antioxidants, we can help our body to defend itself.

**Examples of food-based antioxidants include:**

- the vitamins (vitamin E, vitamin C, and beta carotene).
- the trace elements that are components of antioxidant enzymes (including selenium, copper, zinc, and manganese).
- some non-nutrients such as ubiquinone (coenzyme Q) and phenolic compounds (e.g., phytoestrogens, flavonoids, phenolic acids, butylated hydroxytoluene [BHT], which is used as a food preservative).

**Foods and oxidative stress**

**Tomatoes:** Tomatoes contain a pigment, lycopene, which is responsible for their red colour, but is also a powerful antioxidant. Tomatoes in all their forms are the major source of lycopene and include tomato products like canned tomatoes, tomato soup, tomato juice and even ketchup. Lycopene is also highly concentrated in watermelon.

**Citrus fruits:** Oranges, grapefruit, lemons and limes possess many natural substances that appear to be important in disease protection, such as carotenoids, flavonoids, terpenes, limonoids and coumarins. Together these phytochemicals act more powerfully than if they were given separately. It’s always better to eat the fruit whole in its natural form, as some of the potency is lost when the juice is extracted.

**Tea:** Black tea, green tea and oolong teas have antioxidant properties. All three varieties come from the plant called Camellia sinensis. Common brands of black tea do contain antioxidants, but by far the most potent is green tea (jasmine tea), which contains the antioxidant catechin. Oolong tea has only 40 per cent as much of the antioxidants found in green tea and black tea has only 10 per cent as much. When green tea is processed (baked and fermented) to make black tea, some of the catechins are destroyed.

**Carrots:** Beta-carotene is an orange pigment isolated from carrots 150 years ago. It is found concentrated in deep orange and green vegetables (the green chlorophyll covers up the orange pigment). Beta-carotene is an antioxidant that has been much discussed in connection with lung cancer rates. The evidence is conflicting, but further research is being done to see if it has a protective effect.

**Conclusion**

Although much of the research that has been done on the effect of diet on cancer has been difficult to conduct and interpret, there is now a good body of evidence to indicate the protective effect of fruit and vegetables on many common cancers, including those of colon, breast, and bladder.

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**Role of Genes**

The metabolic processes that produce antioxidants are controlled and influenced by an individual’s genetic make-up and the extra environmental factors.
"If [children with autism] have lower glutathione, they would reach a toxicity earlier than someone with higher levels"

"[Researchers] found changes in three genes more often in the children with autism"
ABSTRACT

Autism is a complex child developmental problem associated with oxidative stress, and brain cells are the most vulnerable to oxidative stress.

Hypothesis

Hyperbaric oxygen (HBOT) is useful in many neurological conditions, but little is known about its effects in autism. The purpose of the study is to determine the effect of hyperbaric therapy at pressures slightly greater than normal on biomarkers of oxidative stress in children with autism. This may help doctors and parents understand the safety of this procedure for this condition.

Method

To evaluate this, changes in blood cell reduced glutathione and lipid peroxides were tested by two special laboratories before and after a one hour exposure at 1.3 atmospheres. Informed consent was obtained by the treating physician for both the blood draw and HBOT.

There were 12 participants in the study (9 boys and 3 girls). Once collected, specimens were processed according to the required protocols provided by the laboratories and shipped overnight.

Before and after HBOT levels of reduced glutathione and lipid peroxides were provided by the participating physician, and then were analyzed using Excel.

Results

The average of post reduced glutathione level was 96% of the pre-exposure level, reflecting a slight trend of increased oxidative stress. The averaged findings for lipid peroxidation showed a slight relief of oxidative stress (3%).

Conclusion

These two observations seem to cancel each other out, but more likely represent no significant trend either way. Overall it did not appear that HBOT significantly altered the oxidative stress for most of the children in the study.
Blood will be drawn immediately prior to a one hour session of hyperbarics (HBT). A catheter will be inserted into a vein and converted to a heparin lock indwelling port for the next blood draw. The child (ages 5-12 years) will then undergo 1 hour of compression at 1.3 atmospheric pressure (4 psi above room air pressure). Supplemental oxygen will be provided to the child.

A second blood draw from the catheter site will be accomplished immediately after the child comes out of the HBT chamber.

These will be sent to the laboratories for evaluation of changes in reduced glutathione and lipid peroxides.

**Eligibility**

* Ages Eligible for Study: 5 Years - 12 Years, Genders Eligible for Study: Both
* Criteria
  * Inclusion Criteria: Children diagnosed with autism ages 5-12 and undergoing hyperbarics
  * Exclusion Criteria: Seizures, acute URI, or inability to ventilate ears

**Location and Contact Information**

Please refer to this study by ClinicalTrials.gov identifier NCT00263367
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**More Information**

Primary Location
Study ID Numbers: ICDRC-22.2005
Last Updated: December 8, 2005
Record first received: November 21, 2005
ClinicalTrials.gov Identifier: NCT00263367
Health Authority: United States: Food and Drug Administration
ClinicalTrials.gov processed this record on 2006-04-13

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**ClinicalTrials.gov Identifier:** NCT00263367

**Purpose**

This study will look at the changes taking place in the blood levels of key markers of oxidative stress. Oxidative stress is the biological equivalent of rust on a car. It changes vital cell chemistry. It is known to occur at high pressure oxygen, but little is known about changes at pressures slightly greater than normal atmospheric pressure.

Hyperbaric therapy is used in a variety of medical conditions. It is being tested in this study only for safety. It is not being assessed for the ability of hyperbaric oxygen to improve the clinical condition of children with autism. This study was felt to be important since autism appears to be associated with oxidative stress and hyperbarics was being used "off-label" for this condition without safety studies.

**Condition**

Autism, Oxidative Stress

**Procedure**

Hyperbaric Oxygen

**Study Type**

Interventional

**Study Design**

Treatment, Non-Randomized, Open Label, Active Control, Single Group Assessment, Safety Study

**Official Title:** Effect of Hyperbaric Therapy on Markers of Oxidative Stress in Children With Autism: A Pilot Study

Further study details as provided by The International Child Development Resource Center:

**Primary Outcomes:**

Reduced glutathione
Lipid peroxides

**Expected Total Enrollment**

10

**Study Start**

October 2005; Expected completion March 2006

**Last Follow-up**

February 2006; Data entry closure: February 2006
Ribbon diagram of the enzyme TIM. TIM is catalytically perfect, meaning its conversion rate is limited, or nearly limited to its substrate diffusion rate.

Activity of Erythrocuprein (Superoxide Dismutase), Biochim Biophys Acta 327, 217, 1973

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In Depth Look: More on Oxidative Stress (continued)

"Compounds which cause oxidation are called oxidants.

In addition, toxins entering the body—pollution, chemicals, heavy metals, insecticides, flavor-enhancers in foods—act as oxidants."

Chemically, oxidation is loss of electrons. When oxidation is rapid, it may result in actual flames, as when wood burns. More slowly, oxidation may result in the bronzed surface of an apple, or the rancidity of oils. The building blocks of cells—fats, proteins, and nucleic acids—are prone to oxidation, which alters structure and function and results in tissue injury.

In addition, toxins entering the body—pollution, chemicals, heavy metals, insecticides, flavor-enhancers in foods—act as oxidants. In excess, nutrients such as copper and iron can act as oxidants. Some of the oxidants which injure cells are called free-radicals, but not all oxidants are free-radicals.

Fortunately, the body has a defense system to neutralize oxidants. The components of this system are antioxidant. These include important dietary antioxidants such as vitamins C, E and A. Other nutrients serving important antioxidant roles include B vitamins, zinc, selenium, magnesium, carnosine and carnitine. The body also manufactures special molecules to quench oxidants. These include glutathione (GSH), metallothionein (MT), melatonin, estrogen, ceruloplasmin, transferrin, and important anti-oxidant enzymes: glutathione peroxidase (GSHPx), superoxide dismutase (SOD), and catalase.

Oxidative stress occurs when oxidants exceed the anti-oxidant defense. Oxidized cell parts in urine, blood and tissue such as brain are direct measurements of oxidative stress. For example, the level of oxidized lipids ("lipid peroxides") in blood is used as a biomarker for oxidative stress.

Indirectly, we also can get an idea about oxidative stress by measuring levels of anti-oxidant nutrients, anti-oxidant molecules such as GSH, or anti-oxidant enzymes. Lower levels of one or more of these anti-oxidant defenses tends to suggest greater oxidative stress. Higher levels of oxidants, such as free-radicals and toxins, suggest higher levels of oxidative stress.
The International Hyperbarics Association, Inc. is a coalition of doctors, parents, patients, corporate chamber-industry professionals, hyperbaric center owners, and above all members who are committed to the cause of medical hyperbarics. Our members come to us from all geographical areas with one common goal—to share their knowledge and information regarding the latest hyperbaric news. Our driving force is our members, who are committed to do all we can “to give life to the world.”