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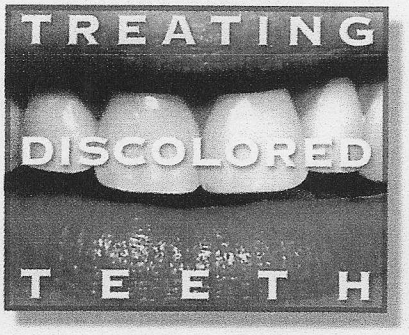

THE EFFECT OF PEROXIDES AND FREE RADICALS ON BODY TISSUES

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ABSTRACT

It is possible that peroxides used to whiten teeth cause damage if used improperly. Oxygen free radicals associated with peroxides are important etiologic agents in the development of many pathological conditions. This report provides background information about the action of peroxides on body tissues—information the dentist can use to perform peroxide bleaching safely.

Peroxides and oxygen free radicals are reactive oxygen species that are formed as natural products in all living systems that use oxygen. Reactive oxygen species are present usually at only very low concentrations because natural antioxidant protective systems prevent their accumulation. Reactive oxygen species in the presence of free metal ions, such as Fe or Cu, react to cause oxidative damage to tissue. The safe use of peroxides in dental practice requires adherence to practices that minimize oxidative damage to oral cavity tissue.

PEROXIDES AND OXYGEN FREE RADICALS: NATURAL PRODUCTS

The most commonly found natural peroxides include lipid hydroperoxide and hydrogen peroxide. Lipid hydroperoxides are formed when oxygen adds to a free radical of a lipid molecule and the alkyl peroxy lipid free radical then abstracts a hydrogen atom from a donor molecule:

$$\dot{L} + O_2 \rightarrow L\dot{O}O + DH \rightarrow LOOH.^{1}$$

Hydrogen peroxide was discovered as a chemical entity in 1818 by Thenard.[1] It was considered as an intermediate in respiration in

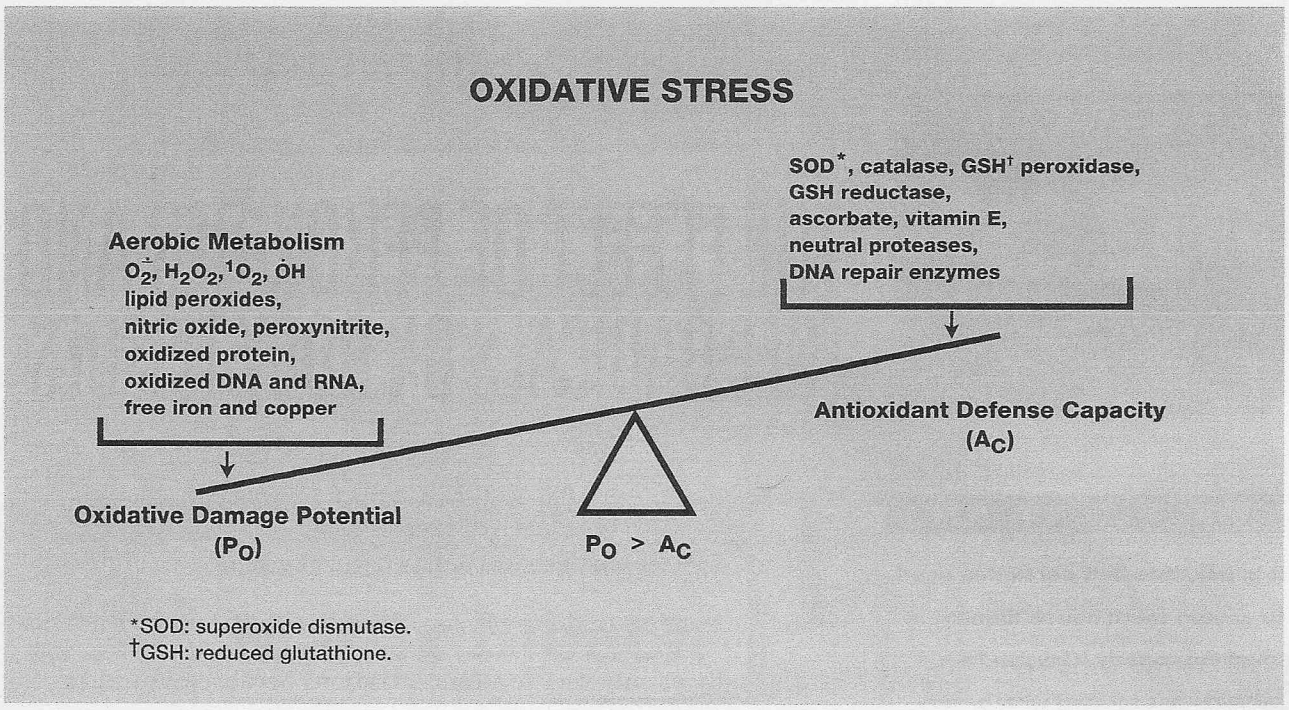


Figure. The concept of oxidative stress.

the 1880s by Hoppe-Seyler as well as by Traube.[1] Catalase, the enzyme that catalytically breaks down H_2O_2 to water and oxygen, was discovered in 1901 by Loew[1]; peroxidase, which breaks down hydrogen peroxide to oxygen and oxidation products, was discovered by Linossier in 1898.[1] More recently, the discovery of superoxide dismutase, or SOD, by McCord and colleagues in 1969[2] opened up a massive amount of research that has brought on a new realization: oxygen free radicals and hydrogen peroxide are important byproducts in oxygen metabolism.

SOD catalyzes the dismutation of superoxide into hydrogen peroxide and oxygen. Certain transition metals, most notably iron and copper, play a very important role in causing oxidative damaging reactions in biological systems. The so-called metal-catalyzed Fenton reactions are important and illustrate the role of iron (in the specific reactions shown) as well as superoxide and H_2O_2.

Certain transition metals, most notably iron and copper, play a very important role in causing oxidative damaging reactions in biological systems.

$$O_2^{\cdot-} + > Fe^{3+} \rightarrow O_2 + > Fe^{2+}$$

$$H_2O_2 + > Fe^{2+} \rightarrow \dot{O}H + OH^- + > Fe^{3+}$$

$$O_2^{\cdot-} + H_2O_2 \xrightarrow{Fe} O_2 + \dot{O}H + OH^-$$

Iron is shown bound to a small molecular weight ligand that allows this transition metal to remain solubilized and participate catalytically in the reaction. Superoxide and hydrogen peroxide are involved in the formation of the hydroxyl free radical, which will react and cause damage to any biological molecule in the immediate vicinity of its site of formation.

OXIDATIVE STRESS

It is widely held that oxygen metabolism poses an oxidative stress on aerobic biological systems. This is simply because it is necessary to have oxygen to sustain life, yet in the metabolism of oxygen to water a certain small fraction (perhaps as much as 2 to 5 percent of the total oxygen) may be diverted to form semireduced forms of oxygen (that is, hydrogen peroxide and superoxide). The semireduced forms of oxygen then participate in oxidative reactions that lead to oxidatively damaging reactions with lipids, proteins and nucleic acids. Thus,

the total semireduced forms of oxygen and their oxidative damage products impose an oxidative damage potential, or P_O, on the biological system.

Nature has evolved many enzymes (such as SOD, catalase and peroxidase) and small molecular weight antioxidants (such as ascorbate, vitamin E and glutathione) to help the body defend itself against the imposed oxidative damage potential. The sum of the total defense systems is referred to as the antioxidant defense capacity, or A_C, of the system. Thus, all aerobic biological systems exist in a metabolic state of equilibrium where A_C counteracts P_O. This equilibrium state is represented for normal aerobic systems in the figure.

Oxidative stress has been classified into three categories: low-level, moderate and intense.

- Low-level oxidative stress is continuously imposed on tissue, and it is likely that it may contribute to aging, in general. The antioxidant status of the tissue (a portion of which can be modified by dietary means) will contribute to the tissue's abilities to handle the continually imposed oxidative stress.
- Moderate oxidative stress may be caused by a rapid, sharp increase in an oxidative insult most likely imposed from external sources—such as, for example, a large (but not lethal) radiation dose or perhaps the administration of Adriamycin. The danger may come if oxidative damage to DNA occurs and is not repaired, thus possibly leading to mutations and possible carcinogenic sequelae. It is possible, but certainly not proven, that repeated peroxide applications to soft tissue over a long period of time may lead to moderate levels of oxidative damage. It should be noted that, in the dental profession's methods of peroxide application, exposure to soft tissue is minimized. In addition, a peroxidase is already present in the mouth[3] that may help decompose the applied peroxides.
- Oxidative stress in the intense category can result in permanent damage or death; an example is that which occurs in a severe stroke. The brain is very sensitive to oxidative damage. Oxidative damage to the brain occurs during stroke. We have introduced newer methodologies, such as salicylate trapping of hydroxyl free radicals,[4] to assess the oxidative damage to the brain that occurs during a stroke.[5] These studies have also led to the discoveries that free radical trapping compounds offer protection from the damage that occurs during a brain stroke[6] and in other neurodegenerative conditions.[7] Animal age influences the animal's ability to recover from a stroke.[6] It is not known if older dental patients, for instance, are more susceptible to tissue damage wrought by applied peroxides than are younger patients, but this possibility should be kept in mind.

IMPORTANT POINTS REGARDING TISSUE RESPONSE TO APPLICATIONS OF OXIDATIVE CHALLENGE.

- Cells normally are subjected to large amounts of oxidative stress because of normal respiration.
- Cells' susceptibility to oxidative stress depends on their age and antioxidant status.
- Inflamed tissues contain phagocytizing leukocytes that produce oxygen free radicals and thus expose surrounding tissues to additive oxidative stress.
- Significant oxidative damage to biological molecules such as proteins and DNA above background levels indicates excessive oxidative stress.

Application of external oxidative stress to tissue experiencing inflammatory reactions is probably unwise.

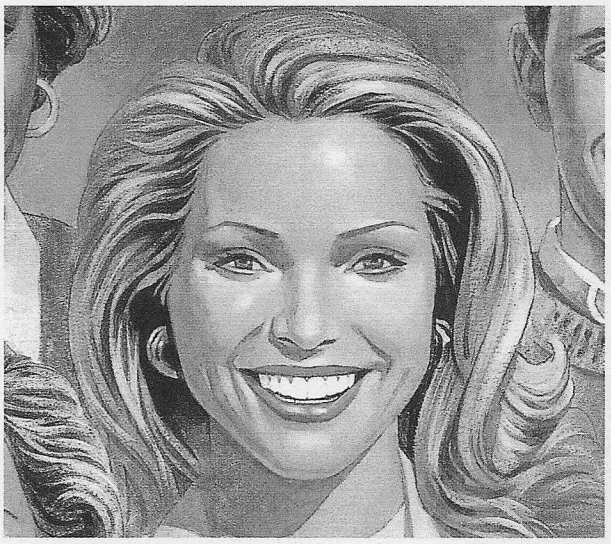
DENTAL USE OF PEROXIDES: IMPORTANT POINTS TO CONSIDER

Dentists should keep in mind several important considerations with regard to potential oxidative damage arising from the application of peroxides (Box).

- As noted earlier, all tissues are subjected to oxidative stress simply because semireduced species of oxygen are produced during aerobic metabolism.
- It is considered that the tissue's susceptibility to oxidative stress damage depends not only on the magnitude of the applied oxidative stress, but also on the

antioxidant status of the tissue per se and possibly on the age of the person.

- Application of external oxidative stress to tissue experiencing inflammatory reactions is probably unwise, as phagocytizing leukocytes produce high levels of oxygen free radicals and, therefore, subject the surrounding tissue to large levels of oxidative stress simply because of this activity.
- If tissue macromolecules such as proteins and DNA have increased levels of oxidative damage as a result of application of external oxidative stress, this indicates that excessive oxidative stress has been applied.



CONCLUSION

It appears that dental professionals have exercised prudent use of peroxides. Feinman recently summarized the use of carbamide peroxide with a custom-fitted carrier by stating, "Five years of nonproblematic treatment for millions of patients leads many dentists to believe that this technique, when controlled by the dentist, serves the public well."[8] ■

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