Editor's Corner

Environmental stimulus package

Potential for a rising oxidative deficit

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A close relationship exists between the multiple systems in the body and the gradual exposure to the environmental influences of oxidative stress, such as airborne particulate matter, pesticides, diet and lifestyle. Over time, exposure to exogenous sources of oxidative stress can ultimately impair both tissue and cellular function and lead to cellular senescence, apoptosis, and the destruction of nuclear chromatin. The effects of oxidative stress from the environment may be muted in some individuals if sufficient anti-oxidant defenses are in place. However, in others, comprised defenses such as those that can occur with immune system dysfunction, can lead to progressive damage in genetic coding and mitochondrial DNA that have been associated with signaling pathway errors and tumorigenesis. Interestingly, "multiple hits" by environmental toxins may be required to lead to system dysfunction or tumor growth. For example, a number of studies have observed that an accumulation of gene mutations with increased age may be necessary to eventually lead to cancers involving the breast or the gastrointestinal tract. Furthermore, the exposure to exogenous agents that may generate the release of reactive oxygen species also may initiate a critical cascade of cell injury. The occurrence of genetic mutations from the initial release of reactive oxygen species can then lead to polymorphisms in key enzymes such as glutathione S-transferase and cytochrome p450 that are vital to protect cells and tissues against oxidative stress. As a result of the loss of these anti-oxidant pathways, further accumulated tissue damage can ensue and the risk of developing significant illness increases further.

Given the intimate relationship between the body and its susceptibility to exogenous sources of oxidative stress, we have highlighted a number of novel studies in this issue of *Oxidative Medicine and Cellular Longevity* that examine specific cellular and tissue responses to endogenous agents and the broad anti-oxidant systems that can mitigate injury during normal physiology and

disease states. Kovacic and Somanathan set the stage for this issue with their opinion paper that describes the biology of a hallucinogenic agent that was an integral part of religious ceremonies by early North American natives and its use remains in our current society, namely mescaline. Their work provides new understanding for the cellular signaling of this agent in the nervous system, its role in structure function relations, and its ties to the hallucinogen psilocybin. In his review article, Flora broadens this perspective in regards to xenobiotics with metal and metalloid exposure. The biological properties of several agents that can lead to human illness are discussed that include copper, cobalt, and arsenic as well as the multiple anti-oxidant systems that can be activated, such as carotenoids, enzymes, hormones, phenolics, minerals, and vitamins. Interestingly, anti-oxidant systems also may play a significant role to prevent toxicity of chemotherapeutic agents. Al-Yahya et al. demonstrate that a naturally occurring branched-chain complex polysaccharide termed Gum Arabic can neutralize acrolein, a reactive metabolite of cyclophosphamide and block bladder toxicity from reactive oxygen species that may provide new direction for chemotherapeutic agents to enhance efficacy but limit toxicity. The ability to block cellular injury during periods of toxic elevated reactive oxygen species release also may be extended to a number systems throughout the body. Santo et al. show that ascorbic acid may be a powerful cytoprotectant in highly sensitive regions of the central nervous system during epilepsy and oxidative stress. Furthermore, in the paper by Mahapatra et al. that examines the effects of the exogenous toxin nicotine on immune cells, extracts from the plant *Ocimum gratissimum* were shown to have high flavonoid and phenolic content that may account for the ability of this agent to reduce super oxide anion generation, lipid peroxidation, and prevent cytotoxicity in immune cell peritoneal macrophages, suggesting that even the inflammatory effects of tobacco smoke that contains at least sixty known carcinogens may be reduced with appropriate anti-oxidant therapy. The efficacy of anti-oxidant therapy is brought to clinical consideration by Tripathi et al. in their paper. These investigators illustrate that administration of L-arginine, which has anti-apoptotic properties and can improve endothelial function, was able to lower serum cholesterol, increase superoxide dismutase function, and enhance the levels of total thiols in patients with cardiac ischemia, suggesting that chronic therapy with L-arginine in these patients may prevent the detrimental

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effects of cardiac insufficiency. Work by Tang et al. adds further insight into the role of tyrosine phosphorylation and the p75 neurotrophin receptor during oxidative stress that may represent future therapeutic targets for disorders such as Alzheimer's disease.

Knowledge of the cellular pathways involved during clinical disease becomes a crucial point in an effort to develop effective clinical therapeutics since presumed cytoprotective agents when prospectively studied do not always prove to be useful or should be employed with caution. Work by Kingsley et al. brings this to light for us in their work that demonstrates that creatine, a popular "energy" supplement during exercise, is ineffective in attenuating oxidative stress during strenuous exercise regimens. As a result, the articles in this issue of *Oxidative Medicine and Cellular Longevity* offer new knowledge for the relationships that tie the environment, exogenous agents, and oxidative stress to multiple systems of the body. The studies illustrate for us that the use of therapeutics against extended stimulus exposure to oxidative stress can only effectively reduce an "oxidative deficit" through the identification of vital cellular pathways that ultimately control cell survival and longevity.