Preface

Recent research efforts aimed at preventing, reducing, or reverting the consequences of pathologic actions by the reactive oxygen species (ROS) on the constituents of the central nervous system have attracted considerable attention by basic and clinical neuroscientists alike. Although knowledge of the pathophysiologic mechanisms of neurodegeneration is most obviously associated with the search for a rational basis and therapies of pure neurologic disorders such as stroke, brain injury, epilepsy, or Parkinson s disease, ever more frequently a role for neurodegenerative mechanisms is proving essential in attempts to elucidate the etiology of psychiatric illnesses. The association of pure psychiatric disorders, for example, depression, with the recovery from traumatic brain injuries has recently been recognized. A similar association appears to exist with the aging-associated neurodegenerative diseases (e.g., Alzheimer s disease). Moreover, the current recognition that depressive symptoms presumably follow particular cellular damage in certain regions of the brain (e.g., the prefrontal cortex) in response to various toxins (e.g., HIV), challenges the distinction between brain trauma and pure psychiatric disorders. A new body of evidence is emerging that suggests that altered gene expression and subtle molecular, structural, and sometimes genetic changes are associated with the occurrence and/or progression of psychiatric diseases.

Unfortunately, the degree of such changes does not necessarily correlate with the severity of the disease, nor with the susceptibility to treatment, which hinders elucidation of the elusive link between neurodegeneration and psychiatric clinical symptoms. There are a few examples that indicate a clear link between structural changes in the brain, such as ventricular enlargement (enlarged ventricle/brain ratio) or hippocampal shrinkage (reduced hippocampal volume, measured using quantitative magnetic resonance imaging), and the psychiatric illness, i.e., schizophrenia and post-traumatic stress disorder (PTSD), respectively. Even in these cases, however, the causal nature of the link has not been proven unequivocally. Nevertheless, these research trends indicate the need for establishing the interactions between the multiple internal and environmental factors and genetic diathesis, leading to specific brain changes, in the development of symptoms historically regarded as psychiatric.

The ROS are being studied for their dual role in biological systems. On the one hand, they are an integral part of essential cellular functioning, i.e., mitochondrial oxidative phosphorylation, and may even be required for successful signal transduction. On the other hand, ROS have clearly been shown to be capable of leading to pathologic cellular modifications, i.e., they may cause oxidative stress. Already two years ago, a special issue of *Restorative Neurology and Neuroscience* (Volume 9, Number 4, 1996) addressed the link between oxidative stress, apoptosis, and brain damage. At the Second International Symposium on Oxidative Stress and Brain Damage, held in Chicago, Illinois, from September 26 to 28, 1997, an integrative and multidisciplinary approach was undertaken to address the link between oxidative stress and neurodegenerative mechanisms.

The results of presented in vitro studies of molecular mechanisms point to the crucial role of mitochondria, cellular ATP levels, and protein kinases in leading the way from oxidative stress to apoptotic cellular demise. Oxidative stress was also shown to be capable of inducing marked alterations in gene expression. The products of some of these genes, e.g., antioxidative enzymes or enzymes such as lipoxygenases and cyclooxygenases, which regulate the insertion of oxygen into biologically active molecules, may, in turn, alter the susceptibility of cells to oxidative stress. Cellular, e.g., neuronal, susceptibility to injurious stimuli, including oxidative stress, can be modified by complex interactions between the endocrine and the nervous systems. Hormones, such as estrogens and the pineal hormone melatonin, have been investigated for their capacity to modify oxidative stress. Although a direct antioxidative action of hormones has been demonstrated in vitro, it is still questionable whether the in vivo levels of these hormones are operative as antioxidants, or whether they alter neuronal vulnerability by utilizing alternative mechanisms, e.g., by stimulating or blocking specific receptors, or by altering a set of integrative biological functions, e.g., circadian neuroendocrine activities. These, and numerous other questions were raised and discussed at the Chicago meeting. The manuscripts in this special issue reflect the spirit of this symposium.

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pathophysiology of neuropsychiatric illnesses. We hope that this interaction will stimulate the opening of new avenues in the search for the most effective and, as yet, unforeseen diagnostic and therapeutic means.

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